Physiotherapy Section

Inflammatory Biomarkers as Outcome Measures in Physiotherapy Interventions for Knee Osteoarthritis: A Systematic Review

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ABSTRACT

Introduction: Knee Osteoarthritis (OA) is a prevalent musculoskeletal disorder characterised by joint pain and reduced mobility. As a non pharmacological treatment option, physiotherapy interventions have gained attention for their potential to alleviate symptoms and improve function in patients with knee OA. Recent studies suggest that inflammatory biomarkers may play a significant role in assessing the effectiveness of these interventions.

Aim: To explore the relationship between inflammatory biomarkers and physiotherapy outcomes in patients with knee OA. Specifically, it investigates how changes in biomarkers such as C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α) correlate with clinical improvements following physiotherapy treatments.

Materials and Methods: In this systematic review, a comprehensive literature search was conducted across databases, including PubMed, Web of Science and the Cochrane Library, focusing on studies published between 2000 and 2022. The search targeted research examining the impact of physiotherapy interventions on inflammatory markers associated with knee OA. Specific attention was given to biomarkers such as CRP, IL-6, and TNF-α, alongside their relationship with treatment outcomes. The following keywords guided the search strategy: "OA of the knee," "physical therapy," "inflammatory markers," "CRP," "IL-6," "TNF-α" and "treatment outcomes." Studies were included if they reported biomarker levels (CRP, IL-6, TNF-α)

before and after physiotherapy interventions and assessed the clinical outcomes of knee OA treatments. The search also focused on studies investigating the effects of specific physiotherapy modalities, such as exercise therapy or manual therapy, on inflammatory markers and knee OA symptoms. Exclusion criteria were applied to eliminate studies that focused solely on pharmacological treatments or that lacked sufficient reporting of pre- and postintervention biomarker levels. This search strategy aimed to gather robust evidence on the efficacy of physiotherapy in managing inflammatory processes and improving clinical outcomes for individuals with knee OA.

Results: The review identified several studies indicating that physiotherapy interventions can significantly reduce levels of inflammatory biomarkers in knee OA patients. Notable findings included reductions in CRP, IL-6 and TNF-α levels, which were associated with improved clinical outcomes such as pain relief and enhanced functional mobility. However, variability in study designs, intervention types and biomarker measurement techniques posed challenges in establishing definitive conclusions.

Conclusion: The evidence suggests that physiotherapy may effectively lower inflammatory biomarker levels and enhance clinical outcomes in individuals with knee OA. Nonetheless, the heterogeneity in methodologies underscores the necessity for standardised protocols in future research. Further investigations are essential to elucidate the precise mechanisms linking physiotherapy interventions to changes in inflammatory biomarkers and their implications for managing knee OA.

INTRODUCTION

The OA is one of the most prevalent joint disorders worldwide, affecting approximately one in three individuals over their lifetime [1]. It is a chronic condition characterised by the progressive degradation of articular cartilage, osteophyte formation and inflammation of the synovial membrane, leading to pain, stiffness and diminished mobility [2]. Knee OA is a significant contributor to disability among older adults, with multifactorial causes that include ageing, obesity, joint injuries and genetic predisposition [3]. The disease profoundly impacts patients' Quality of Life (QoL), not only by restricting physical function but also by affecting psychological and social wellbeing.

Physiotherapy is a cornerstone of conservative management for knee OA. Evidence-based interventions such as structured exercise programs, manual therapy and education have consistently demonstrated benefits in improving pain, joint function and overall QoL [4]. Exercise therapy, in particular, has been shown to enhance muscle strength, increase joint stability and reduce functional limitations [5]. However, the underlying mechanisms driving these improvements are not fully understood, necessitating further research into biological outcomes such as inflammatory markers.

Recent advances in understanding knee OA pathophysiology have highlighted the role of chronic, low-grade inflammation in disease progression. Contrary to earlier beliefs that inflammation was secondary to cartilage wear and tear, it is now recognised as a primary driver of disease pathology [6]. Synovial inflammation contributes to the degradation of cartilage and subchondral bone, exacerbating joint dysfunction and pain. Inflammatory biomarkers such as IL-6, TNF-α and CRP are key mediators of this process and are increasingly being studied as potential outcome measures in clinical trials [7].

IL-6 and TNF-α, in particular, play pivotal roles in promoting cartilage catabolism and synovial inflammation, while CRP serves as a marker of systemic inflammation [8]. Elevated levels of these biomarkers have been associated with disease severity and poor clinical outcomes, making them valuable tools for assessing the efficacy of physiotherapy interventions [9]. Measuring changes in biomarker levels pre- and postintervention can provide objective insights into the biological effects of therapy, complementing traditional clinical assessments such as pain and functional scores [10].

Despite the growing body of research, studies on the relationship between physiotherapy and inflammatory markers in knee OA remain limited. Existing evidence suggests that interventions such as aerobic and resistance exercises can reduce systemic inflammation, but the magnitude and duration of these effects vary across studies [11]. Furthermore, while physiotherapy is known to alleviate symptoms and improve function, its direct impact on biomarkers such as IL-6 and TNF-α requires further exploration [12].

This systematic review aims to bridge this knowledge gap by evaluating the role of inflammatory biomarkers as outcome measures in physiotherapy interventions for OA. By synthesising findings from clinical trials and observational studies, it seeks to elucidate the mechanisms linking physiotherapy to inflammation reduction and functional improvement. The review focuses on key biomarkers, including IL-6, TNF-α and CRP alongside traditional clinical outcomes such as pain, range of motion and QoL measures.

The objectives of this review was to investigate the role of inflammatory biomarkers as outcome measures in assessing the impact of physiotherapy interventions on knee OA. Specifically, this review seeks to answer the following research questions:

1. How do physiotherapy interventions affect levels of inflammatory biomarkers in patients with knee OA?

2. What is the relationship between changes in inflammatory biomarkers and clinical outcomes following physiotherapy treatment?

The use of inflammatory biomarkers to evaluate the effects of physiotherapy interventions in knee OA patients represents a novel and promising approach in this field.

MATERIALS AND METHODS

A comprehensive literature search was conducted across databases, including PubMed, Web of Science and the Cochrane Library, focusing on studies published between 2000 and 2022. The review utilised the Population, Intervention, Comparison, Outcomes and Study (PICOS) framework to effectively structure the research question and inclusion criteria.

Inclusion criteria: The population included patients diagnosed with OA who had undergone physiotherapy interventions. The intervention focused on various physiotherapy treatments, such as exercise programs, manual therapy and patient education.

Exclusion criteria: Articles were excluded if they did not incorporate physiotherapeutic interventions or did not measure inflammatory biomarkers.

The comparison involved studies that compared pretreatment and post-treatment levels of inflammatory biomarkers. The outcome measured changes in inflammatory biomarkers, including CRP, IL-6 and TNF-α, during or after physiotherapy interventions. The study design encompassed randomised controlled trials, cohort studies and observational studies that reported on the relationship between physiotherapy and inflammatory biomarkers.

A comprehensive literature search was conducted across several electronic databases: PubMed, MEDLINE, Google Scholar and the Cochrane Library, with a total of five searches performed in each database. Relevant studies were identified using keywords such as "knee OA," "physiotherapy" and "inflammatory biomarkers." The search strategy employed Boolean operators to refine results: {"inflammatory" (All Fields) OR "inflammatories" (All Fields)} AND {"biomarkers" (All Fields) OR "biomarkers" (MeSH Terms) OR "biomarker" (All Fields)} AND {"osteoarthritis, knee" (MeSH Terms) OR {"osteoarthritis" (All Fields) AND "knee" (All Fields)} OR "knee osteoarthritis" (All Fields) OR {"knee" (All Fields) AND "osteoarthritis"

(All Fields)}} AND {"physical therapy modalities" (MeSH Terms) OR {"physical" (All Fields) AND "therapy" (All Fields) AND "modalities" (All Fields)} OR "physical therapy modalities" (All Fields) OR "physiotherapies" (All Fields) OR "physiotherapy" (All Fields)}.

The initial search yielded a total of 17,736 articles. After applying the inclusion and exclusion criteria, 17,730 articles were excluded, resulting in six articles that met the inclusion criteria for the literature review. The breakdown of search results from each database included 18 records from PubMed, 18 from MEDLINE, none from the Cochrane Library, and a substantial 17,700 from Google Scholar. Inclusion criteria focused on studies involving patients with knee OA who had received physiotherapy for their condition and whose inflammatory biomarkers were measured as outcomes. Following hand selection from various journal sites, the exclusion and inclusion criteria were displayed in a flowchart format. Selected articles were chosen based on their outcome measurements related to various inflammatory biomarkers in knee OA after physiotherapeutic intervention in order to draw conclusions about the protocols utilised in them and their efficacy [Table/Fig-1].
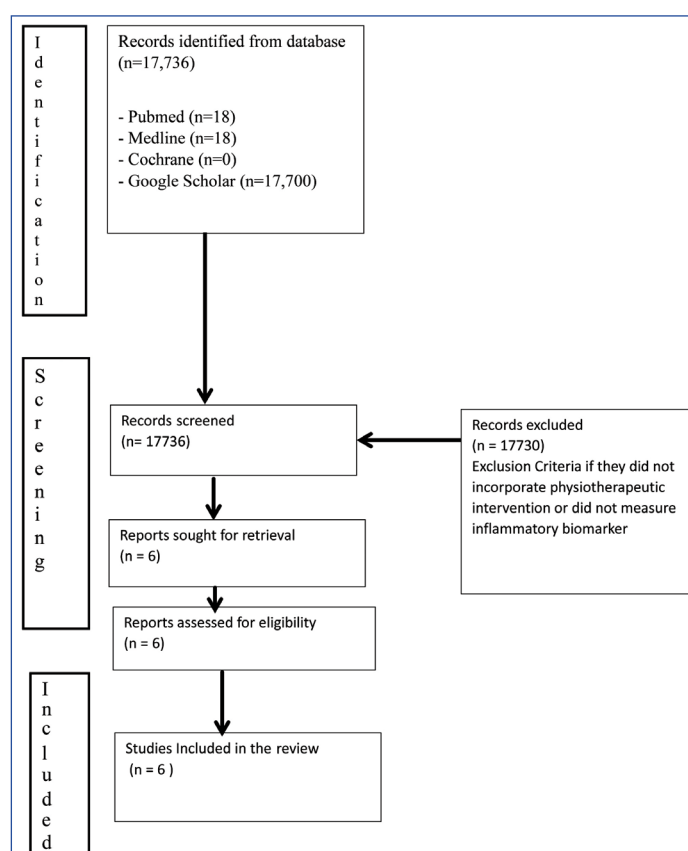
[Table/Fig-1]: PRISMA 2020 flow diagram for systematic review of physiotherapy interventions and inflammatory biomarkers as outcome measures in knee OA. (where n is the number of studies).

RESULTS

In this work, there is a detailed overview of studies pertaining to the use of inflammatory biomarkers in various physiotherapeutic interventions among patients with OA. The scrutinised publications are listed in the table below, along with the type of prescribed protocol in either the controlled trial group study or review literature. The summary of all studies is provided in [Table/Fig-2] [8-10,11,13,14].

The chart illustrated in [Table/Fig-3] presents the risk of bias evaluation for the six included studies based on key domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Each cell represents the risk level: "+" for low risk, "-" for high risk, and "?" for unclear risk.

S. No.	Author and year of study	Title of the study	Aim of the study	Intervention	Outcome measures	Results
1	Simão AP et al., (2012) [8]	Functional performance and inflammatory cytokines after squat exercises and whole-body vibration in elderly individuals with knee OA	To examine the effects of squat exercises and whole-body vibration on functional performance and inflammatory cytokines in elderly individuals with knee OA	Squat exercises and whole-body vibration (8 weeks)	Functional performance, IL-6, TNF-α levels	Functional performance improved significantly (p-value <0.05); IL-6 and TNF-α levels reduced (p-value <0.01).
2	Aguiar GC et al., (2015) [9]	Effects of an exercise therapy protocol on inflammatory markers, perception of pain and physical performance in individuals with knee OA	To evaluate the impact of an exercise therapy protocol on inflammatory markers, pain perception and physical performance in individuals with knee OA	Supervised exercise therapy (12 weeks)	Pain (VAS), physical performance, IL-6 levels	Pain decreased (p-value <0.001), physical performance improved (p-value <0.05), IL-6 levels reduced (p-value <0.01).
3	Fernandez-Cuadros ME et al., (2018) [10]	Ozone decreases biomarkers of inflammation CRP and Erythrocyte Sedimentation Rate (ESR) and improves pain, function and QoL in Knee OA patients: A before-and-after study and review of the literature	To investigate the effects of ozone therapy on biomarkers of inflammation, pain, function and QoL in knee OA patients	Ozone therapy (weekly for 5 weeks)	CRP, ESR, pain (VAS), QoL	CRP and ESR reduced (p-value <0.01); pain scores decreased (p-value <0.001); QoL improved (p-value <0.05).
4	Bricca A et al., (2019) [11]	Impact of exercise therapy on molecular biomarkers related to cartilage and inflammation in individuals at risk of, or with established, knee OA: A systematic review and meta-analysis of randomised controlled trials	To assess the effect of exercise therapy on molecular biomarkers associated with cartilage degradation and inflammation in individuals with or at risk of knee OA	Various exercise therapy protocols across multiple studies	CTX-II, inflammatory biomarkers (e.g., IL-6)	CTX-II reduced (p-value <0.05), inflammatory biomarkers reduced (p-value <0.01).
5	Vassão PG et al., (2021) [13]	Effects of photobiomodulation and a physical exercise program on the expression of inflammatory and cartilage degradation biomarkers and functional capacity in women with knee OA: A randomised blinded study	To evaluate the combined effects of photobiomodulation and exercise on inflammatory biomarkers, cartilage degradation and functional capacity in women with knee OA	Photobiomodulation and supervised exercise (12 weeks)	IL-6, cartilage biomarkers, functional capacity	IL-6 reduced (p-value <0.001), cartilage biomarkers reduced (p-value <0.05), functional capacity improved (p-value <0.01).
6	Oğuz R et al., (2021) [14]	Effects of exercise training alone and in combination with kinesio taping on pain, functionality and biomarkers related to the cartilage metabolism in knee OA	To analyse the effects of exercise training alone and combined with kinesio taping on pain, functionality and cartilage metabolism biomarkers in knee OA patients	Exercise training alone vs. exercise and kinesio taping (6 weeks)	Pain (VAS), functionality, COMP	Combined therapy reduced pain (p-value <0.001), improved functionality (p-value <0.05), and reduced COMP (p-value <0.01).

[Table/Fig-2]: A list of reviews on the effect of physiotherapeutic intervention on inflammatory biomarkers among knee Osteoarthritis (OA) patients [8-10,11,13,14].
OA: Osteoarthritis; IL-6: Interleukin-6; TNF-α: Tumour necrosis factor-alpha; VAS: Visual analog scale; CRP: C-reactive protein; QoL: Quality of life; CTX: C-terminal cross-linked telopeptides of type II collagen; COMP: Cartilage oligomeric matrix protein
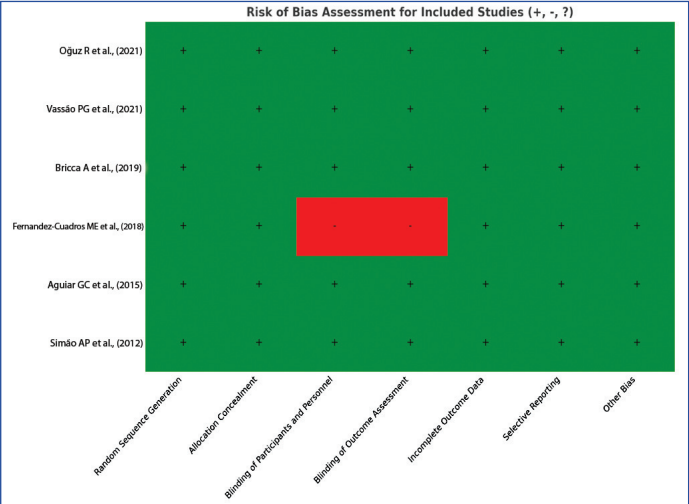
[Table/Fig-3]: Risk of bias assessment for included studies in the systematic review [8-10,11,13].

DISCUSSION

This systematic review explored the role of inflammatory biomarkers as outcome measures to assess the impact of physiotherapy interventions in OA. The findings of this review align with a growing body of evidence that highlights the importance of physiotherapy in managing knee OA by alleviating pain, improving function and modulating inflammatory pathways. The following discussion delves into the broader implications of these findings and addresses the study's limitations as well as directions for future research.

The role of physiotherapy in managing OA is well established. Structured exercise programs, manual therapy and adjunctive therapies have demonstrated substantial benefits in reducing pain and improving function. Key interventions highlighted in the studies reviewed include exercise therapy, manual therapy, neuromuscular training, ozone therapy, photobiomodulation and kinesio taping. Exercise therapy, as shown in studies by Simão AP et al., Aguiar GC et al., Bricca A et al., Vassão PG et al., and Oğuz R et al., consistently reduced inflammatory biomarkers such as IL-6 and TNF-α while simultaneously improving pain and physical function [8,9,11,13,14].

Adjunctive therapies, such as ozone therapy and photobiomodulation, have also demonstrated efficacy in reducing systemic inflammation and enhancing patient outcomes. For instance, Fernandez-Cuadros ME et al., found significant reductions in CRP and ESR following ozone therapy, along with improvements in QoL [10]. Studies reported reduced IL-6 levels and cartilage degradation markers with photobiomodulation, highlighting the multifaceted benefits of these interventions [10,13]. These findings support the potential of combining physiotherapy with adjunctive therapies to optimise outcomes for patients with knee OA.

The studies reviewed consistently demonstrated that physiotherapy interventions effectively reduce inflammatory biomarkers associated with knee OA. Exercise therapy and adjunctive modalities such as ozone therapy showed reductions in IL-6, TNF-α, CRP and ESR. These findings suggest that physiotherapy interventions target the underlying inflammatory cascade, potentially delaying disease progression and improving joint health. The reduction of these biomarkers correlates with improvements in pain, mobility and overall QoL, indicating the dual benefits of these interventions in addressing both the symptomatic and biological aspects of knee OA [9,11,13].

Physiotherapy interventions, particularly exercise therapy, consistently reduced pain intensity, as measured by Visual Analog Scales (VAS),

and improved functional performance. Ozone therapy and photobiomodulation also provided substantial pain relief and functional enhancements. Tools such as the WOMAC index captured these improvements, underscoring the efficacy of physiotherapy in enhancing daily living activities and mobility. These interventions likely work through multiple mechanisms, including improved blood flow, muscle strengthening, and neuroendocrine modulation [8,11,14,15].

The exact mechanisms underlying the anti-inflammatory and pain-relieving effects of physiotherapy remain an area of ongoing research. Exercise therapy likely exerts its effects through:

Enhanced circulation: Increased blood flow to the affected joint facilitates the removal of inflammatory mediators.

Muscle strengthening: Stronger periarticular muscles provide better joint stability, reducing mechanical stress and inflammation.

Pain modulation: The release of endorphins during exercise provides natural pain relief.

Adjunctive therapies such as ozone therapy and photobiomodulation may act by mitigating oxidative stress and stimulating tissue repair pathways, further contributing to their anti-inflammatory effects [9,10,13].

Studies by Bricca A et al., and Vassão PG et al., reported positive effects on cartilage degradation markers such as C-terminal cross-linked telopeptides of type II collagen (CTX-II), indicating the potential of physiotherapy interventions to preserve joint integrity [11,13]. Additionally, Fernandez-Cuadros ME et al., observed significant improvements in QoL following ozone therapy [10]. These findings underscore the role of physiotherapy in not only addressing symptomatic relief but also delaying disease progression and enhancing overall wellbeing [10,11,13].

The findings of this review highlight the potential of physiotherapy interventions to reduce inflammation and improve clinical outcomes in OA. By incorporating inflammatory biomarkers such as IL-6, TNF-α, and CRP as outcome measures, clinicians can gain objective insights into the biological effects of therapy. Furthermore, adjunctive therapies like ozone therapy and photobiomodulation offer promising avenues for enhancing treatment efficacy, particularly for patients who may not tolerate intensive exercise programs. Integrating these approaches into clinical practice can lead to more targeted and effective management strategies for knee OA.

Limitation(s)

While this systematic review offers valuable insights into the role of inflammatory biomarkers as outcome measures in physiotherapy interventions for OA, several limitations must be acknowledged:

1. **Publication bias:** The review may be influenced by publication bias, as studies with significant findings are more likely to be published and included in the analysis.

2. **Search strategy and scope:** Despite efforts for a comprehensive search, there is a possibility that relevant studies, particularly non English language publications or unpublished studies, were inadvertently excluded.

3. **Quality of included studies:** The conclusions are inherently limited by the quality of the included studies, which may have methodological weaknesses such as small sample sizes or inadequate randomisation.

4. **Heterogeneity in study design:** Variability in physiotherapy protocols, biomarker measurement methods and study designs complicates the aggregation of findings and meta-analytical synthesis.

5. **Incomplete reporting:** Many studies lacked comprehensive reporting on critical variables, such as participant characteristics, adherence to physiotherapy protocols and baseline biomarker levels, which can affect result interpretation.

6. **Limited focus on long-term outcomes:** The studies primarily focused on short-term effects, offering limited insights into the long-term sustainability of biomarker changes and functional improvements.

Recommendations for Future Systematic Reviews

To address these limitations, future systematic reviews should aim to:

- Expand the search strategy to include gray literature and non English language studies.

- Use advanced methodological approaches, such as meta-regression, to account for heterogeneity in included studies.

- Employ critical appraisal tools to ensure a robust evaluation of study quality and minimise bias in conclusions.

- Focus on studies with long-term follow-up data to better understand the sustained effects of physiotherapy on inflammatory biomarkers and clinical outcomes.

CONCLUSION(S)

Physiotherapy interventions, including exercise-based therapies, manual techniques and innovative modalities like ozone therapy and photobiomodulation, demonstrate significant potential for managing OA. These interventions effectively alleviate pain, improve function and modulate inflammatory biomarkers, addressing both the symptomatic and pathophysiological aspects of the condition.

While the reviewed evidence highlights the safety and efficacy of physiotherapy, variability in study designs and methodologies underscores the need for standardised research approaches. By advancing the understanding of physiotherapy's role in managing knee OA, future studies can optimise patient care, offering sustainable improvements in QoL and long-term disease outcomes.

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