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Cytokine levels in Fibromyalgia patients and the effects of physiotherapy tools: A systematic review and metanalysis

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INTRODUCTION

Review question / Objective To analyze the evidence of cytokine levels in patients with fibromyalgia compared to healthy subjects. Specific objectives are:
a) analyzing which proinflammatory and anti-inflammatory cytokines are present in fibromyalgia;
b) studying which cytokines are present in muscle tissue and plasma in fibromyalgia patients;
c) examining which physiotherapy tools have been used to investigate the effects that these can have on cytokines in fibromyalgia patients.

Rationale The etiology of Fibromyalgia syndrome still needs to be better understood and is still under investigation, as the results found in different studies are contradictory. Fibromyalgia is a syndrome with a multifactorial etiology that develops depending on genetic predisposition, personal experiences, emotional and cognitive factors, and the individual's ability to cope with stress.

Although FM is traditionally a non-inflammatory condition, current evidence suggests that other factors contribute to its pathogenesis, such as inflammatory, immunological, and endocrine factors. In fibromyalgia, there is increasing evidence of inflammatory mech-anisms of neurogenic origin in peripheral tissues, the spinal cord, and the brain. Cytokines/chemokines, lipid mediators, oxidative stress and various plasma-derived factors underlie the inflammatory state in fibromyalgia.
This inflammation is closely related to the activation of both the innate and adaptive immune systems that produce an inflammatory cascade of neuropeptides, cytokines, and chemokines, which may play an essential role in the pathophysiology of fibromyalgia. Cytokines function as messengers of the immune system and have a regulatory role in inflammation and are essential in a brief form; the problem comes when there is prolonged exposure to them, leading to chronic low-grade inflammation. Cytokines are classified into proin-flammatory and anti-inflammatory cytokines. The central proinflammatory cytokines are IL-1, IL-2,

IL-6, IL-8, IL-12, TNF-alfa and IFN, while the central anti-inflammatory cytokines are IL-4, IL-10, IL-13, and TGF. The proinflammatory to anti-inflammatory cytokines ratio is vital in determining disease outcomes. Current research has shown that cytokine levels are imbalanced in the human body and that the proinflammatory to anti-inflammatory cytokines ratio is critical in determining disease outcome.
Current research has shown that cytokine levels are imbalanced in fibromyalgia patients. There is an imbalance between proinflammatory and anti-inflammatory cytokines, with more proinflammatory cytokines such as TNF-alfa, IL-1RA, IL-6, and IL-8.

Condition being studied Fibromyalgia [FM] is characterized by chronic, widespread musculoskeletal pain with multiple tender points and generalized tenderness with muscle stiffness, joint stiffness, sleep disturbances, fatigue, mood, cognitive dysfunction, anxiety, depression, general tenderness, and inability to perform daily life activities. Regarding prevalence, it is estimated that 4% of the world's population is affected by FM, mainly in women aged 20-55 years.
The diagnosis is only clinical and consists of a complete assessment based on the 1990 American College of Rheumatology (ACR)te criteria of three consecutive months of widespread pain and "tender points" of pain on palpation. In 2010, the ACR updated the criteria with two new parameters, and in 2016, the criteria were further revised to decrease the likelihood of misdiagnosis.

METHODS

Search strategy For this systematic review, we followed the protocol according to the standards and guidelines of the PRISMA statement for systematic reviews and meta-analyses, which aims to improve the reporting of future systematic reviews. The methodological protocol was registered after the present work.
Before starting the present systematic review, a search of different databases was carried out to verify the existence of recent reviews on the topic in question. Subsequently, several searches were performed using different combinations of the key terms, including "cytokines AND fibromyalgia" and "cytokines AND fibromyalgia AND physiotherapy." It used the search equation ["cytokines and Fibromyalgia and Physiotherapy"] to focus the search on studies that used physiotherapy tools as an intervention and analyzed their possible effects on cytokines in fibromyalgia patients. The same Medical Subject Headings [MeSH] terms were used to improve the specificity of the search.
A series of filters were established and included in each database to perform the current searches.

Participant or population Subjects with a diagnosis of fibromyalgia according to the ACR 1990. Women of working age [an intervention group performing a physiotherapeutic intervention.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included Clinical trials and randomized controlled clinical trials using a placebo or control group.

Eligibility criteria Publications in the last ten years [from 2013 to 2023]; Written in English or Spanish; Cytokine analysis.

Information sources The databases Pubmed, Scopus, Web of Science, Cochrane Register, and ScienceDirect were searched. A search was also made in second-line sources, doctoral theses, journal articles, etc., in Dialnet; and Teseo, but there were no results.
These searches were carried out from December 2022 to March 2023.

Main outcome(s) During the initial stage of the search, 318 studies were identified from different data-bases. After removing duplicates, 302 studies remained.
To refine the selection, we applied date filters (2013-2023) and chose to select only clinical trials and randomized clinical trials, which were available in English or Spanish. After reviewing the titles and abstracts, 49 studies that did not fit the study topic were discarded, leaving ten studies for analysis. Of these, after a detailed reading, two studies were eliminated for inconclusive results, leaving a total of eight studies that met the inclusion criteria and were subjected to a qualitative analysis.
To carry out date and study type filters, we used database filters. To search for duplicates and perform the inclusion or exclusion of studies, we used an intelligent research collaboration platform called Rayyan, which optimizes efficiency in elaborating systematic reviews by facilitating the organization and classification of relevant studies to be considered.

Data management A reviewer working independently carried out both the study selection process and the data extraction process for each of the final articles. Subsequently, the results obtained were analyzed by two independent reviewers [IHB and EUD]. In case of doubt or

disagreement between the reviewers, they were jointly assessed until a consensus was reached.

Quality assessment / Risk of bias analysis Risk of bias is a tool developed by the Cochrane Collaboration to assess the method-ology of scientific evidence. It is useful in systematic reviews for the individual analysis of included CTs and RCTs. In this sense, the present systematic review has followed the Cochrane Handbook 5.1.0 [12] to assess the risk of bias.
The Cochrane Handbook 5.1.0 presents six levels of bias: selection bias, conduct bias, detection bias, attrition bias, reporting bias, and other bias. Each level has one or more specific items in a Risk of Bias table, and each item includes a description of what happened in the study and an assessment where the assignment of "low risk," "high risk," or "unclear risk" of bias is included.

Strategy of data synthesis The synthesis methods used in the present review are the eligibility criteria that were determined in material and methods sysnthesis and the analysis of methodological quality using the PEDro scale, which is based on the Delphi checklist developed by Verhagen. The checklist has a total of 11 items. The first item refers to external validity and is not considered for the final score; items 2-9 refer to internal validity, and items 10 and 11 indicate whether the statistical information provided by the authors allows for an adequate interpretation of the results.
Therefore, the maximum score is 10 points, and the minimum is 0. Only items that are answered affirmatively are scored. Studies with a score of 9-10 were of excellent methodological quality, 6-8 of good quality, and 5 of fair or acceptable quality. The PEDro scale will be found in more detail in the results section of the synthesis.
Further to the synthesis measures, we assessed whether the studies included in the analysis met their objectives set at the start of the study. Of the eight studies included in this review, all of them met the objectives proposed at the outset. Regarding the homogeneity of the experimental and control groups of the studies, it was observed that in six of the eight articles, the groups were homogeneous, and the subjects were matched. However, in one of the studies, participants were not matched according to BMI, and the experimental group had higher BMI and blood pressure than the control group, and some participants had concomitant metabolic syndrome. In another study, the plasma analysis performed on the participants was not homogeneous, as the experimental group consisted of 75 subjects, while the control group had only 25 subjects.

Subgroup analysis The GRADE system was followed to measure the assessment of the certainty of the evidence, which defines the quality of evidence as the degree of confidence we have that the estimate of an effect is adequate to make a recommendation. In classifying the quality of evidence, the GRADE system establishes four categories: high, moderate, low, and very low. From the present systematic review, five of the eight studies have a high quality of evidence, and three studies a moderate quality.

Sensitivity analysis Statistical analysis of the meta-analysis was performed using the Review Manager software [RevMan 5.4; Cochrane Collaboration, Oxford, UK]. A meta-analysis of the pre-dominant variables using the same parameter and measurement scale was carried out using the random effects model, in which it was assumed that the effect of the treatments was not the same in all the studies included in the model. For this, the original values of each study [Mean and Standard Deviation or Median and interquartile range] were taken as reference. The effects of the experimental interventions against the comparison groups [controls, placebo, relaxation therapy, and healthy women without fibromyalgia] were presented as mean differences and their confidence intervals, taking a 95% CI as reference. The heterogeneity of the studies was evaluated using the I2 statistic, where values greater than 35% were heterogeneous. The variance between studies was calculated using Tau-square [Tau2]. The significance level was set at 0.05 for statistically significant effects.

Language restriction No language restriction.

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Keywords cytokines; fibromyalgia; physiotherapy; metanalysis.

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