ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.72692
Rheumatol Q 2025;3(1):6-11

THE ROLE OF CHEMOKINES IN FIBROMYALGIA

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Abstract

Aim: Chemokines are cytokines that cause chemotaxis to leukocytes and stem cells in inflammation and homeostasis. Fibromyalgia (FM) is characterized by widespread chronic pain and somatic symptoms. The role of immun mediators in the pathogenesis of FM is the topic of recent researches and current evidence supports that chemokines are important in the syndrome's pathogenesis. In our study, the importance of some chemokines and their receptors in FM and their relationship with pain and disease severity are analyzed.

Material and Methods: This is a cross-sectional analytic study. Our study included 40 female patients with FM (American College of Rheumatology, 2016) and 40 healthy controls matched for age and body mass index (BMI). C-C motif chemokine receptor 3, chemokine (C-C motif) 4 (CCL4), and macrophage-derived chemokine (MDC) levels were measured in the blood samples of the participants using the enzyme-linked immunosorbent assay. Pain and disease severity in FM patients were evaluated with a visual analog scale (VAS, 0-10 cm) and Fibromyalgia Impact Questionnaire (FIQ), respectively.

Results: The groups were similar in terms of age (p=0.19) and BMI values (p=0.109). C-reactive protein (p=0.013), MDC (p=0.016), and CCL4 (p=0.026) values were higher in the FM group. The mean VAS of the FM group was 7.5±2.5 cm, while the FIQ was 61.1±14.9.

Conclusion: MDC and CCL4 chemokines can be used as helpful parameters in diagnosing FM with moderate sensitivity and specificity. High levels of chemokines in the FM group support the role of chemokines in the etiopathogenesis of disease through immunomodulation in the nervous system.

Keywords: Fibromyalgia, chemokine, CCR3, CCL4, MDC

INTRODUCTION

Chemokines constitute a family of cytokines. With the rapid development of research in recent years, these 50 separate members serve as mediators that play a regulatory role in normal biological and pathological processes. Chemokine receptors are G-protein-dependent structures that transmit intracellular signals. The immune system's response to inflammatory events such as antigenic and autoimmune reactions depends on the chemokines directing and activating leukocytes at the right time (1,2). As a result of chemokines binding to the appropriate receptor, cells stimulated by signal transmission lead to tissue damage, inflammation, or migration to the required area (chemotaxis) (3).

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Received: 20.11.2024 **Accepted:** 06.01.2025 **Publication Date:** 21.03.2025
Cite this article as: Koca TT, Seyithanoğlu M, Sakınmaz F. The role of chemokines in fibromyalgia. Rheumatol Q. 2025;3(1):6-11

The settlement of leukocytes in tissues constitutes an important step in inflammation and the host response to infectious situations. In summary, chemokines are cytokines that induce chemotaxis of leukocytes and stem cells in inflammation and homeostasis (3-6). There are several chemokine subfamilies (e.g., CXC, CC, C, and CX3C) defined according to the positioning of cysteine residues (7,8).

Disability due to chronic pain is common worldwide. We know that our immune system has a role in the pathogenesis of many pain syndromes. Involvement of the immune system may occur with autoantibodies, as in rheumatoid arthritis, or with cytokines, chemokines, and other inflammatory mediators. Immune cells (T cells, B cells, autoantibodies, microglia) play a role in immune-mediated pain. By elucidating this relationship, targets for treatment can be developed or optimized in diseases such as fibromyalgia (FM) that present with chronic pain (9).

FM is a multifaceted disease, and its clinical presentation includes comorbidities. Each comorbidity is a separate condition. Genetic, environmental, neurohormonal factors, and pathophysiological factors including inflammation are held responsible for the background of the disease. New data are obtained every day regarding the etiopathogenesis of FM. Cytokines and chemokines, lipid mediators, oxidative stress, and plasma-derived factors, support the existence of inflammatory/immunological pathways in FM development (9). It has been shown that the levels of some inflammatory cytokines, such as (IL-1RA, IL-6, and IL-8), and some chemokines have increased in recent years (9-11). In our study, the role of some chemokines and receptors [C-C motif chemokine receptor 3(CCR3), Chemokine 4 (CCL4), macrophage-derived chemokine (MDC)] and their relationship with pain and disease severity was analyzed.

MATERIAL AND METHODS

Study Design and Data Source

Our study was planned as cross-sectional. Forty female patients with FM (American College of Rheumatology, 2016) and 40 healthy volunteers with similar age and BMI distribution were included in the study. Pain and disease severity in FM patients were evaluated with a visual analog scale (VAS, 0-10 cm) and fibromyalgia impact questionnaire (FIQ) (12), respectively. Blood samples were taken during outpatient admission.

After centrifugation for 10 minutes, it was stored at temperatures below -80 degrees Celsius. Those with a history of chronic inflammatory rheumatic disease, infection, malignancy, hypothalamic-pituitary axis pathology, cognitive disorder, neurological disease, psychiatric disease, acute trauma, and surgical procedures were excluded from the study.

Biochemical Analysis

In blood samples from both groups, chemokine, and receptor levels; CCR-3, MDC, and CCL-4 were calculated using an enzyme-linked immunosorbent assay (ELISA) method according to the manufacturer's protocol (13-15). The kits were provided by Wuhan Fine Biotech (Wuhan, China). The characteristics of the kits are listed in Table 1. C-reactive protein (CRP, cut-off: 0-5) and erythrocyte sedimentation rate (ESR, cut-off: 0-30) values from the archive files of the patients within the last 3 months were checked and recorded for exclusion criteria. Patients with active infection were excluded.

Statistical Analysis

It was performed using the Statistical Package for Social Sciences (SPSS ver. 20), and $p<0.05$ were considered statistically difference. Normal distribution of the data was determined using the Shapiro-Wilk, the Kolmogorov-Smirnov test, and histogram columns. Numerical data with normal distribution are given as mean ± standard deviation; those with non-normal distribution are given as median (minimum/maximum). Independent Samples t-test was used to compare two groups. The Spearman correlation test was used.

A receiver operating characteristic (ROC) curve was applied for MDC and CCL4 diagnostic tests, and the threshold value for these values was manually selected based on both the highest sensitivity and the highest 1-1 specificity.

RESULTS

Forty female FM with a mean age of 46.1±9.8 years and 40 healthy control females with a mean age of 42.8±12.8 years were included in our study (p=0.19). BMI values were similar

Table 1. The characteristics of the kits

Kit name	Catalog number	Intra assay CV	Inter-assay CV	Detection range	Sensitivity
CCR3	EH2089	<8%	<10%	0.313-20 ng/mL	0.188 ng/mL
MDC	EH0223	<8%	<10%	62.5-4000 pg/mL	37.5 pg/mL
CCL4	EH0067	<8%	<10%	31.25-2000 pg/mL	18.75 pg/mL

CCR3: C-C chemokine receptor type 3, MDC: Macrophage derived chemokine, CCL4: C-C motif chemokine 4, CV: Coefficient of variation

in both groups (p=0.109). CRP (p=0.013), MDC (p=0.016), and CCL4 (p=0.026) levels were higher in patients with FM (Figure 1A, B). The mean VAS value of the FM group was 7.5±2.5 cm, while the FIQ value was 61.1±14.9. A comparison of the group data is summarized in Table 2.

In the correlation analysis, the VAS value was positively correlated with ESR (p=0.019) and FIQ (p<0.01). The CCL4 value was positively correlated with age (p=0.037), MDC (p=0.003), and BMI (p=0.003). Age and BMI (p=0.037) were found to be positively correlated. None of the 3 chemokines and receptor levels were not found to correlate with ESR and CRP. Only positive values are shown in Table 3.

In ROC analysis for the serum MDC levels was statistically significant (area under the ROC curve: 0.681, confidence interval: 0.562-0.800, p=0.005). High values indicated FM, with a threshold of >442,9 sensitivity of 67%, and specificity of 60% (Figure 2A). ROC analysis for the serum CCL4 levels was statistically significant (area under the ROC curve: 0.644, confidence interval: 0.522-0.766, p=0.026). High values indicated FM, with a threshold of >190,1 sensitivity of 62.5%, and specificity of 60% (Figure 2B).

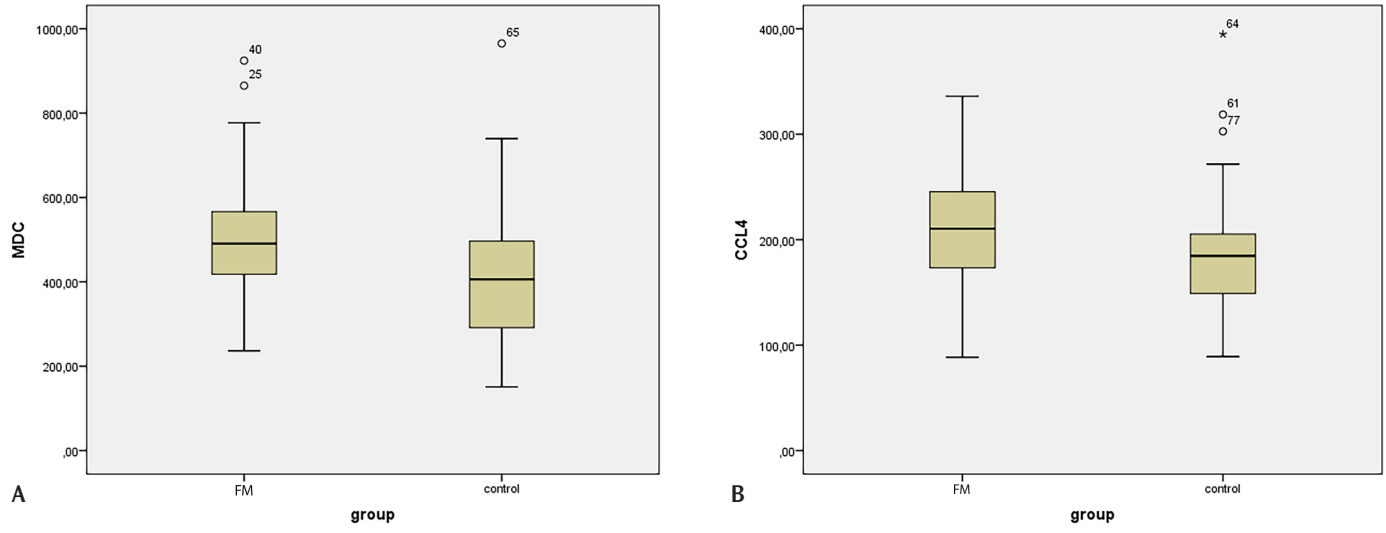

Figure 1. MDC (A) and CCL4 (B) levels in the study groups
MDC: Macrophage-derived chemokine, CCL4: C-C motif chemokine 4, FM: Fibromyalgia

Table 2. Comparison of parameters of groups

	FM (n=40) Mean ± SD/Med., (min.-max.)	Control (n=40) Mean ± SD/Med., (min.-max.)	p-value
Age (year)	46.1±9.8	42.8±12.8	0.19
BMI (kg/m^2)	26.9±4.2	25.2±5.17	0.109
ESR (mm/h)	11±8.3	11.1±9.1	0.95
CRP (g/dL)	3.2 (1.4-31)	3 (1-13)	0.013**
VAS (0-10 cm)	7.5±2.5	-	
FIQ	61.1±14.9	-	
CCR3 (ng/mL)	2.7±0.9	2.9±2.4	0.75
MDC (pg/mL)	506.6±145.4	419.2±172.0	0.016*
CCL4 (pg/mL)	210.46 (88.51-336)	184.6 (89.15-394.84)	0.026**

*Independent Samples t-test, **Mann-Whitney U test, p<0.05, statistically significance. FM: Fibromyalgia syndrome, BMI: Body mass index, FIQ: Fibromyalgia impact questionnaire, VAS: Visual Analog Scale, ESR: Erythrocyte sedimentation rate, CRP: C- reactive protein, CCR3: C-C chemokine receptor type 3, CCL4: C-C motif chemokine 4, MDC: Macrophage derived chemokine, Med.: Median, min.-max.: Minimum-maximum, SD: Standard deviation

Table 3. Inter-parameter correlation analysis

	r	p***
Age-CCL4	0.234	0.037***
Age-BMI	0.289	0.011***
VAS-ESR	0.380	0.019***
VAS-FIQ	0.764	<0.01***
ESR-CRP	0,380	0.019***
MDC-CCL4	0.330	0.003***
CCL4-BMI	0.329	0.003***

***Spearman's correlation analysis, p<0.05, stastitically significance. Only positive results were shown in Table 3. BMI: Body mass index, FIQ: Fibromyalgia impact questionnaire, VAS: Visual analog scale, ESR: Erythrocyte sedimentation rate, CRP: C- reactive protein, CCR3: C-C chemokine receptor type 3, CCL4: C-C motif chemokine 4, MDC: Macrophage derived chemokine

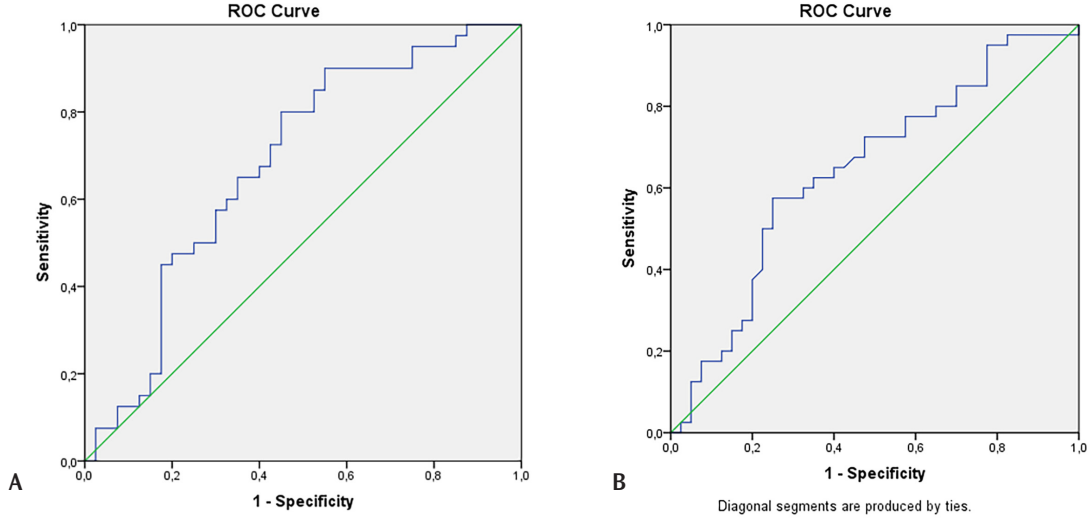

Figure 2. ROC analysis of MDC (A) and CCl4 (B) for fibromyalgia
ROC: Receiver operating characteristic, MDC: Macrophage derived chemokine

DISCUSSION

The etiology of FM is not well understood and we do not have hematochemical or instrumental tests for its diagnosis yet. Key features in the FM clinic include widespread pain and tenderness, sleep disturbance, fatigue, cognitive problems and psychological distress. Inadequate processing of pain and other sensory inputs occurs in the nervous system and is explained by sensitization. FM is classified as a central sensitivity syndrome. There is sufficient evidence supporting neurogenic inflammation in peripheral and central tissues (9-11). With the effect of both the inherent and acquired immunity, chemokines, cytokines, and various neuropeptides are involved in the process. These explain clinical findings such as swelling and dysesthesia, and may affect central symptoms including fatigue and cognitive changes. Emotional or stress-related psychological mechanisms may trigger neurogenic inflammation in FM (16).

Chemokines have important roles in many biological processes occurring in the body. The chemokine superfamily includes many ligands and receptors. However, this idea has changed after understanding the key roles of chemokine subgroups in the cellular network organization and functions that shape the immune system (17,18). Chemokines are effective in leukocyte-endothelial cell relations, T and B cell maturation, immune control, formation of tolerance and immunity, T-B cell transmission, and the formation of the primary immune response. In addition, they play a role in dendritic cell functions, T cell differentiation and functions, effector T cell response in inflammatory diseases, mucosal immunity, and events that suppress the host immune response by various viruses, including HIV-1 (17). Apart from inflammation, it has biological activities such as angiogenesis, hematopoiesis, and an increased host response to tumors (19). They act in the brain not only

as immunomodulators but also as potential modulators of neurotransmission and neuroendocrine regulation (20).

Today, the etiopathogenesis of the different clinical findings seen in FM remains to be elucidated. Both the central and peripheral nervous systems have an effect on disease development. Although the disease was classified as non-inflammatory before, we see that the immune system is also involved in the pathogenesis. Current data suggest that central nervous system dysfunction, which causes pain, mood, and sleep disturbances observed in FM, may be related to immune system changes (21).

FM is characterized by increased systemic inflammatory biomarkers and innate cellular response. Increased chemokines and proinflammatory cytokines in serum are thought to contribute to systemic inflammation (22). In our study, CRP, MDC, and CCL4 levels were significantly higher in the FM group than in the healthy group. Additionally, MDC and CCL4 were positively correlated with each other. We found that CCL4 values increase with advanced age and high BMI. Our study supports the idea that changes occur in the immune-inflammatory pathways in FM. Current studies focus on chemokines and cytokines that regulate pathogenesis in physiological and pathological conditions. When we look at similar studies in the literature, García et al. (23) found that monocytes from patients with FM are deregulated, releasing higher amounts of eotaxin, MDC, and growth-regulated-oncogene than healthy controls.

In meta-analysis by Andrés-Rodríguez et al. (24), an imbalance between upregulated pro-inflammatory and immune-regulatory cytokines was observed. In another study by Andrés-Rodríguez et al. (25) they observed that the mindfulness-based stress reduction method reduces the disease severity by affecting cytokines and chemokines (IL-6, IL-10, CXCL8) associated with psychological symptoms in FM. They found that this technique provides clinical benefits by regulating immune-inflammatory pathways. In our study, disease severity parameters (VAS, FIQ) were not related to MDC, CCL4, and CCR3. Chemokines, chemokine receptors, and CRP were high in the FM group, regardless of disease severity (FIQ). Only the VAS value was positively correlated with ESR. The correlation between ESR and VAS values in the study can be explained by the fact that pain complaints are more common in those with higher ESR values, and vice versa. We may say that neuroimmune processes take part in FM symptoms.

There is growing evidence that the peripheral nervous system and systemic inflammation are as effective as central mechanisms in the formation of widespread pain in FM (26). In the study by Khamisy-Farah et al. (27), high CRP, mean platelet volume, and platelet-lymphocyte ratio were observed in FM patients, along with a low lymphocyte count. Aktürk and Büyükavcı (28) observed that the neutrophil/lymphocyte ratio was high in the FM group. Systemic inflammatory response appears to be high in FM. In our study, we found the CRP value to be significantly higher in the FM group. CRP and ESR values were not correlated with chemokines.

In the meta-analysis conducted by O'Mahony et al. (29), high levels of pro-inflammatory and anti-inflammatory cytokines and eotaxin were detected in the peripheral blood of FM patients (30). In the study by García et al. (30) (n=17), inflammatory chemokines were found to be similar in the FM group and the control group. There is increasing evidence that proinflammatory cytokines and genetic variant connections in pain-related genes play a role in the development of FM and the severity of the disease (31,32). It is thought that the roles of FM-related central/peripheral neuroimmune processes in disease development and severity may be related to genes.

Many different mechanisms play a role in studies on the pathogenesis of FM. Also, chemokine levels are affected by factors, such as signaling, environmental influences, genetic predisposition, and various physiological and pathological conditions. Infections, tissue trauma, inflammatory conditions, immune signals, hormones, genetic factors, diet and lifestyle, environmental pollution, allergens, stress, age, and obesity can affect chemokine levels. It is difficult to explain clearly the mechanism by which chemokine levels are affected in FM patients. The study's limitations include the sample size and the omission of considering the use of medications that may affect the results.

CONCLUSION

A wide spectrum of symptoms seen in FM, including widespread pain, cognitive dysfunction, emotional distress, sleep disturbance, and chronic fatigue, appear to be related to central and peripheral neuroimmune pathways in the pathogenesis. The best-defined pathological mechanisms related to FM are changes in central pain pathways and emotional states that trigger or worsen symptoms. Studies in the last decade, to elucidate the etiopathogenesis of FM, reveal that inflammatory mediators, cytokines, peptides, and chemokines also have a role in the disease process. In our study, the high levels of CRP and chemokines (MDC and CCL4) in the FM group support the role of neuroimmune and inflammatory pathways in the pathogenesis of the disease. Elucidating the etiopathogenesis of FM will guide the management of different symptoms and the development of treatment approaches.

Ethics

Ethics Committee Approval: Our study was carried out by the Declaration of Helsinki and approved by Sütçü İmam University Faculty of Medicine Clinical Trials Ethics Committee (approval number: 02, protocol number: 86, dated: 14.02.2022).

Informed Consent: A written informed consent was obtained from the participants.

Footnotes

Authorship Contributions

Concept: T.T.K., Design: T.T.K., Data Collection or Processing: F.S., Analysis or Interpretation: M.S., Literature Search: M.S., Writing: T.T.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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