Study of serum monocyte chemoattractant protein-1 as a marker of disease activity in rheumatoid arthritis patients

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Introduction
Rheumatoid arthritis (RA) is a chronic systemic disease that primarily targets the synovium, leading to synovial inflammation and proliferation, loss of articular cartilage, and erosion of juxta-articular bone.

Objective
The aim of the work was to assess the role of serum monocyte chemoattractant protein-1 (MCP-1) as a marker of disease activity in RA and its correlation with different disease parameters.

Patients and methods
We assessed serum MCP-1 level in 40 RA patients and 20 age-matched and sex-matched healthy controls. We also assessed different clinical and laboratory disease parameters in RA patients – namely, swollen joint count, tender joint count, erythrocyte sedimentation rate, C-reactive protein (CRP), rheumatoid factor, anti-cyclic citrullinated peptide (ACCP), and 28-joint Disease Activity Score (DAS-28) (CRP). We correlated serum MCP-1 with disease activity and different disease parameters.

Results
Serum MCP-1 was significantly higher (P = 0.001) in the patient group (mean = 414, SD = 508.97) than in the control group (mean = 77.25, SD = 16.58). Serum level also correlated significantly with rheumatoid factor (P = 0.004), swollen joint count (P = 0.004), and with DAS-28 CRP score (0.034). There was no significant correlation between MCP-1 and tender joint count, erythrocyte sedimentation rate, CRP, or radiographic changes.

Conclusion
Serum MCP-1 is a useful biomarker in monitoring RA activity.

Keywords:
Activity marker, monocyte chemoattractant protein-1, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease that primarily targets the synovium, leading to synovial inflammation and proliferation, loss of articular cartilage, and erosion of juxta-articular bone [1].

The natural history of RA is complex and affected by a number of factors, including age of onset, sex, genotype, phenotype (i.e. extra-articular manifestations or variants of RA), and comorbid conditions, which make for a truly heterogeneous disease. There is no simple way to predict the clinical course. It is important to realize that as many as 10% of patients will undergo a spontaneous remission within 6 months. However, the vast majority of patients will exhibit a pattern of persistent and progressive disease activity that waxes and wanes in intensity over time [2].

Monitoring disease activity at regular, short-term intervals and appropriate modifications of disease modifying anti-rheumatic drug (DMARD) therapy to establish and maintain control of disease result in improved radiographic and functional outcomes in patients with RA [3].

Several indicators of disease activity are typically assessed in clinical trials of therapeutic agents in patients with RA. Among them, the most often measured are swollen (SJC) and tender joint counts (TJC), pain, patient and evaluator global assessments, acute phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], duration of morning stiffness, fatigue, measures of function (e.g. the health assessment questionnaire (HAQ)), and health status [4].

However, ESR and CRP are nonspecific indicators of inflammation that can be elevated due to age, anemia, and the presence of immunoglobulins, and that can be unexpectedly low or even normal in patients with active disease, possibly due to underlying genetics [5].

Protein biomarkers can provide complementary, objective, and reliable measurements reflecting underlying pathophysiological processes and may provide important information on disease state [6].

Predominant cell types involved in synovial inflammation include activated T cells, monocytes/macrophages, and neutrophils [7].

Increased cellularity in the RA synovium is accompanied by increased expression of adhesion molecules involved in cell trafficking and of proinflammatory mediators such as cytokines and chemokines [8].

Chemokines (chemotactic cytokines) are small heparin-binding proteins that direct the movement of circulating leukocytes to sites of inflammation or injury [9]. They segregate into four families on the basis of differences in structure and function. The largest family consists of CC chemokines. The most thoroughly characterized CC chemokine is monocyte chemoattractant protein-1 (MCP-1), termed 'chemokine ligand CCL2' [10].

Aim of the work

The aim of this study was to determine serum concentrations of MCP-1 in patients with RA and its correlation with disease activity, and other patient and disease related parameters.

Patients and methods

This study was conducted on 40 patients fulfilling the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria of RA and 20 age-matched and sex-matched healthy individuals. The patients were recruited from the outpatient clinic or the inpatient ward of Internal Medicine Department at Alexandria Main University Hospital. Other chronic inflammatory conditions such as systemic lupus erythematosis (SLE), mixed connective tissue diseases (MCTDs) and polymyositis, coronary artery disease, sepsis, and malignancies were excluded.

All patients were subjected to detailed history taking, full clinical examination, and laboratory evaluation, including complete blood count, ESR, CRP, albumin, rheumatoid factor (RF), anti-cyclic peptide antibody (ACPA), and serum MCP-1, which was assessed using enzyme-linked immunosorbent assay. Radiological evaluation included radiography of both hands in the anteroposterior view. Disease activity was evaluated through the 28-joint Disease Activity Score (DAS-28) CRP score.

The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsiniki and informed consent was obtained from each patient.

Statistical analysis

Data were checked, entered, and analyzed using the SPSS 18 software package (SPSS Inc., Chicago, Illinois, USA). The normally distributed data were expressed as mean ± SD. Multiple group comparisons were made using one-way analysis of variance. Univariate correlations between study variables were calculated with Spearman's rank correlation coefficients (r). P values less than 0.05 were considered significant.

Results

Demographic, clinical, and laboratory data are illustrated in Table 1.

Table 1 Distribution of the studied cases according to different parameters

Disease parameter	Range	Mean ± SD
Number of patients	40	
Age (years)	23.0–70.0	46.90 ± 11.68
Sex (female/male)	25/15	
Duration of disease (years)	0.10–30.0	7.36 ± 9.08
Swollen joints	0.0–10.0	1.35 ± 2.28
Tender joints	0.0–24.0	7.13 ± 7.12
Joint deformities [*n* (%)]	8 (20.0)	
Extra-articular manifestations [*n* (%)]		
Nodules	5 (12.5)	
Hematologic	20 (50.0)	
Pulmonary	2 (5.0)	
ESR	16.0–146.0	81.90 ± 32.76
CRP	2.15–148.0	34.65 ± 35.47
Albumin	2.20–3.90	3.23 ± 0.40
RF	8.0–3240.0	262.56 ± 580.52
<15	8 (20.0%)	
≥15	32 (80.0%)	
ACPA	2.80–1500.0	312.66 ± 306.76
<20	9 (22.5%)	
≥20	31 (77.5%)	
MCP-1	50.0–2000.0	414.0 ± 508.97
DAS-28 score	1.69–6.15	3.94 ± 1.21
Imaging (radiographic changes of the hand) [*n* (%)]	17 (42.5%)	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCP-1, monocyte chemoattractant protein-1; RF, rheumatoid factor.

In the present study, the range of serum MCP-1 in the case group ranged from 50 to 2000 pg/ml, with a mean of 414 and an SD of 508.97, whereas the range in the control group was from 50 to 115 pg/ml, with a mean of 77.25 and an SD of 16.58 (Fig. 1), and this difference was of high statistical significance ($P < 0.001$).

There was a positive correlation between MCP-1 level in RA patients and their DAS-28 (CRP) score and such correlation was statistically significant ($P = 0.034$) (Fig. 2).

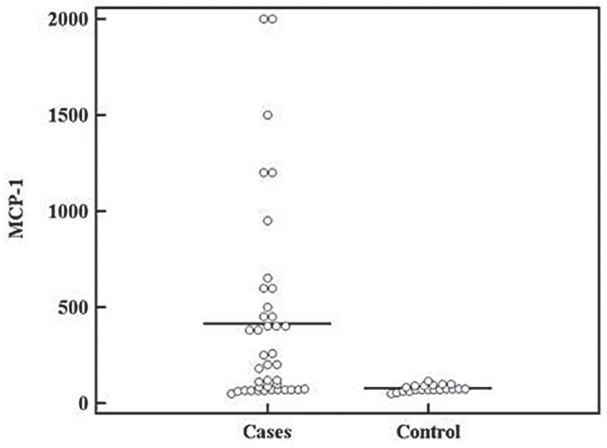
As regards other disease parameters, there was a statistically significant positive correlation between MCP-1 level and RF ($P = 0.004$) (Fig. 3), and between MCP-1 level and SJC ($P = 0.004$) (Fig. 4); however, there was no significant correlation between MCP-1 level and ESR ($P = 0.941$), CRP ($P = 0.151$), ACPA ($P = 0.519$), TJC ($P = 0.142$), and radiographic changes (Table 2).

Table 2 Correlation between monocyte chemoattractant protein-1 level with different parameters in the case group

Disease parameter	MCP-1 level	
	r_s	*P*
DAS-28 score	0.335*	0.034*
ESR	−0.012	0.941
CRP	0.232	0.151
RF	0.450*	0.004*
ACPA	0.105	0.519
Tender joints	0.236	0.142
Swollen joints	0.443*	0.004*

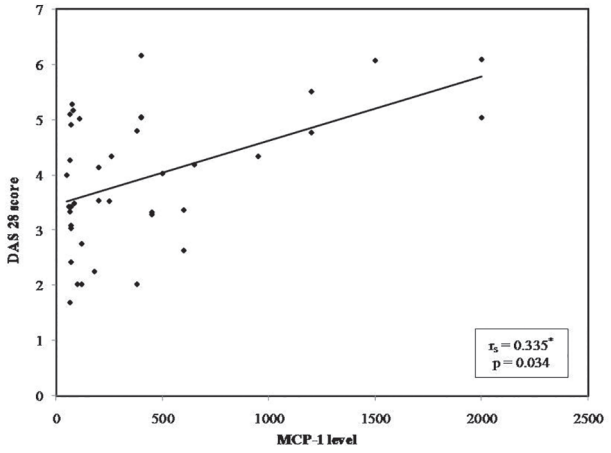
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCP-1, monocyte chemoattractant protein-1; RF, rheumatoid factor; * significant correlation.

Figure 1



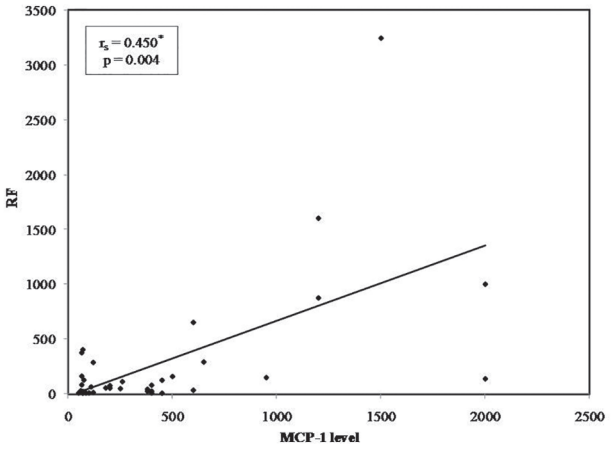
Comparison between the two studied groups according to monocyte chemoattractant protein-1 (MCP-1).

Figure 2



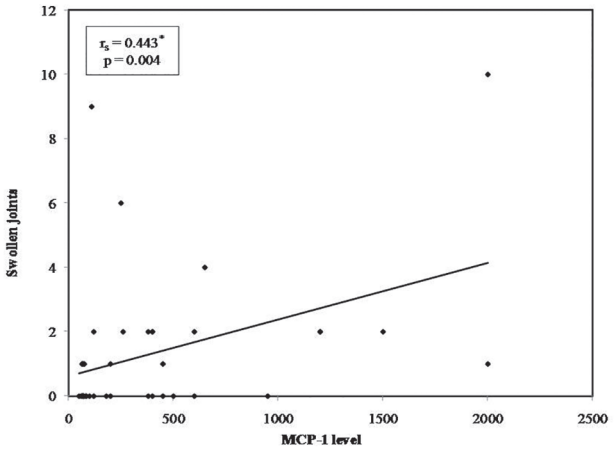
Correlation between monocyte chemoattractant protein-1 (MCP-1) level with DAS-28 score in the case group.

Figure 3



Correlation between monocyte chemoattractant protein-1 (MCP-1) level with rheumatoid factor (RF) in the case group.

Figure 4



Correlation between monocyte chemoattractant protein-1 (MCP-1) level with swollen joints in the case group.

Discussion

The management of RA has changed radically over the last 15 years with the introduction of new drugs and treatment strategies and with the emergence of new concepts of disease severity, treatment targets, and means of evaluating treatment effects.

In particular, the necessity to evaluate disease activity using an objective and accurate instrument has been demonstrated. In clinical practice, the DAS-28 has gained widespread use in the monitoring of disease activity of patients with RA treated with synthetic and biological disease modifying antirheumatic drugs [11]. There is, however, no consensus on the optimal DAS version to be used. DAS-28 (CRP) was developed as a modification of DAS-28-ESR, which had also previously been developed as a modification of the original DAS [12].

Using CRP for calculation of the DAS-28 is an attractive alternative to ESR for several reasons. First, CRP is very sensitive to short-term changes in inflammation.

Second, CRP is more accurate as an indicator of inflammation compared with ESR, the latter being influenced by a number of unrelated factors, such as age, sex, anemia, fibrinogen levels, and hypergammaglobulinemia [13].

Two key findings have emerged from the current literature. First, the DAS-28-CRP has been validated with respect to functional and radiographic progression, with a validation profile similar to that based on ESR [14]. Second, subsequent data analyses from large cohort databases showed that disease activity tended to be underestimated when DAS-28-CRP was used [15].

Macrophages infiltrated into synovium play an important role in joint destruction in inflammatory joint diseases. Synovial fluid from RA, osteoarthritis (OA), gout, and traumatic arthritis contained MCP-1. Levels of MCP-1 were significantly correlated with levels of interleukin-1b (IL-1b), IL-6, and IL-8 in the culture supernatants of synovia from RA. This cytokine network contributes to the immunopathogenesis of RA [16].

According to our results, serum MCP-1 levels were higher in the case group (ranged from 50 to 2000 pg/ml with a mean of 414 and an SD of 16.58) than in the control group (ranged from 50 to 115 pg/ml with a mean of 77.25 and an SD of 16.58) and this difference was of high statistical significance ($P < 0.001$).

There was also a statistically significant correlation between serum MCP-1 level and disease activity as evaluated using DAS-28 (CRP).

Increased levels of serum and synovial fluid MCP-1 was a prominent finding in multiple studies investigating the correlation not only between MCP-1 and RA but also between MCP-1 and other inflammatory arthritides.

Stankovic and colleagues in their study on 30 RA and 15 OA patients stated that MCP-1 was found in increased amounts in the serum of patients with RA compared with OA patients. The values were significantly greater in RA patients with more active disease. Moreover, a positive correlation was found between RA synovial fluid concentrations and synovial fluid leukocyte numbers [17].

Koch and colleagues investigated the production of MCP-1 in serum and synovial fluid of 80 arthritic patients and concluded that MCP-1 levels were significantly higher in synovial fluid from RA patients compared with synovial fluid from OA patients, or from patients with other arthritides. Serum MCP-1 was also elevated in both RA and other inflammatory arthritides, but levels were higher in RA [18].

Furthermore, to investigate the usefulness of MCP-1 as a marker of disease activity, Liou *et al.* [19] designated a DAS-28 (MCP-1) version of the DAS-28 score by incorporating MCP-1 data into the calculated equation for DAS-28 and concluded that DAS-28-MCP-1 score correlated highly with DAS-28 at 0, 1, 3, and 6 months of the 48 newly diagnosed RA patients and significantly with clinical and laboratory measures of disease activity – namely, TJC, SJC, and ESR – but weakly with CRP.

However, the correlation between serum MCP-1 level and different parameters of RA was variable between different studies. Our results showed a statistically significant positive correlation between MCP-1 level and both RF and SJC, and no significant correlation with ESR, CRP, ACPA, TJC, and radiographic changes.

Here is a summary of some studies investigating the correlation between serum MCP-1 level and different disease parameters (Table 3) [20,21].

This variability between the different studies as regards the correlation between serum MCP-1 and different disease parameters may be attributed to several causes.

First, the difference in the inclusion criteria of each study, as some included newly diagnosed DMARD-

Table 3 Summary of the studies investigating the correlation between serum monocyte chemoattractant protein-1 level and different rheumatoid arthritis disease parameters

Study	SJC	TJC	ESR	CRP	RF	ACPA	DAS	Radiography
This study	+	−	−	−	+	−	+	−
Koch *et al.* [18]					−			
Stankovic *et al.* [17]							+	
Liou *et al.* [19]	+	+	+	−			+	
Ellingsen *et al.* [20]	+		−	−				
Klimiuk *et al.* [21]	−		+	+			+	

+, positive correlation; −, no correlation; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCP-1, monocyte chemoattractant protein-1; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.

untreated RA patients only, whereas others included regularly DMARD-treated RA patients as well. The effect of DMARDs on serum MCP-1 level versus their effect on other disease parameters is still to be investigated, in addition to the different sample size of each study.

Second, the different ethnicity between the studies, which may affect the prevalence of seropositivity to RF and ACCP as may the duration since the onset of arthritic activity as was observed in studies of different ethnicities [22–24].

Third, the different factors influencing the level of ESR and CRP, independent of the disease activity.

Fourth, the accuracy of clinical SJC and TJC assessments has issues of reproducibility and may not differentiate between tender joints in fibromyalgia and the swelling of OA, fibrous thickening, or obesity. Patient assessments may be confused with comorbid symptoms and fluctuations of mood.

According to our results, anemia of chronic disease was the most common extra-articular manifestation. Möller *et al.* [25] performed a longitudinal population-based cohort study of 4377 RA patients. They found that erosions progressed significantly faster in patients with anemia, independent of clinical disease activity and other indicators of disease severity. They concluded that anemia in RA appears to capture disease processes that remain unmeasured by established disease activity measures, and may help to identify patients with more rapid erosive disease.

In our study, we found no correlation between serum MCP-1 level and joint destruction. The concept of disease activity is based upon the state of the underlying inflammatory response and may be distinguished from the destructive process that leads to irreversible damage of the joint. Structural damage is cumulative and irreversible. The degree of damage is closely linked to inflammation and hence to disease activity, but is also associated with degeneration and repair. Inflammation may ultimately remit, and hence inflammatory biomarkers; however, structural damage is irreversible [26].

In view of our results, serum MCP-1 is a promising biomarker for assessment of disease activity in patients with RA, and may be involved in activity scores either DAS-28 upcoming modifications or multibiomarker disease activity multibiomarker disease activity (MBDA) tests.

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Conflicts of interest
There are no conflicts of interest.

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