Published in final edited form as:

Biomark Med. 2015 August ; 9(8): 723–729. doi:10.2217/BMM.15.40.

Monocyte chemotactic protein-1 elevation prior to the onset of rheumatoid arthritis among women

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Abstract

Objective—To examine monocyte chemotactic protein-1 (MCP-1) concentration and future rheumatoid arthritis (RA) risk, and investigate effect modification by human leukocyte antigen-shared epitope (*HLA-SE*) and several lifestyle factors.

Methods—We conducted a nested case-control study using stored plasma samples from the Nurses' Health Studies. Each pre-RA case was matched to three controls ($N_{\text{case}} = 220$, $N_{\text{control}} = 675$). Odds ratios (OR) for RA associated with MCP-1 concentration and interactions with *HLA-SE*, smoking, BMI and alcohol intake were estimated.

Results—MCP-1 concentration was associated with both seropositive and seronegative RA, in particular <5 years of blood draw (OR: 2.42), and among *HLA-SE* positive (OR: 2.05). No interactions with smoking, BMI or alcohol were detected.

Conclusion—MCP-1 was associated with risk of RA, especially among *HLA-SE* positive, but did not differ by smoking status, BMI or alcohol intake.

Keywords

chemokine; monocyte chemotactic protein-1; obesity; rheumatoid arthritis; smoking

Rheumatoid arthritis (RA) is known to develop over time, with autoantibodies and cytokine abnormalities detectable in the blood years prior to the onset of clinical symptoms [1]. Smoking and obesity have been demonstrated to increase the risk of developing RA [2,3], whereas moderate alcohol intake (<5 g/week) has been associated with decreased risk of RA [3,4]. Both smoking and obesity are associated with increased systemic inflammation, with elevated levels of C-reactive protein, IL-6 and TNF- α in the blood [5–8], and moderate

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The authors declare that they have no conflicts of interests.

Financial & competing interests disclosure: The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

alcohol intake has been associated with lower levels of these biomarkers of inflammation [9,10]. We and others have previously reported that circulating plasma levels of the cytokines IL-6, TNFR2 (a proxy for TNF- α) are elevated years prior to RA onset [1,11].

In a past case-control study that utilized banked samples in Sweden, monocyte chemoattractant protein-1 (MCP-1) was higher among 92 patients who later developed RA compared with controls, in particular among those who developed anticitrullinated peptide antibody (ACPA)-positive RA [12]. MCP-1 is a C-C chemokine that is ubiquitously produced, in particular by adipocytes. MCP-1 plays a major role in inflammation through attracting monocytes and macrophages, which are key cells in RA pathogenesis [13]. Like TNF- α and IL-6, MCP-1 unleashes complex pathways of chemokine- and cytokine-mediated systemic inflammation [14]. We thus hypothesized that there may be modification of the relationship between plasma levels of MCP-1 and the future risk of RA, according to an individual's BMI, alcohol intake and smoking history. In the current study, we examined MCP-1 levels among pre-RA cases compared with controls, and whether these levels varied according to potentially proinflammatory (BMI and smoking) and anti-inflammatory (alcohol intake) lifestyle factors.

Methods

Study design & population

We conducted a nested case-control study using blood samples from Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII), cohorts of US female nurses aged 30–55 years in 1976 and aged 25–42 years in 1989, respectively. All participants completed biennial questionnaires regarding diseases and lifestyle. In 1989–1990, 32,826 NHS participants and, in 1996–1999, 29,611 NHSII participants provided plasma samples. We excluded women with cancer (except nonmelanoma skin cancer) at blood draw, as cancer could influence both lifestyle and MCP-1. This study was approved by the Partners' Healthcare Institutional Review Board and return of a completed questionnaire was accepted as informed consent and approved by the review board.

Identification of RA cases

Women who developed RA were identified from self reports of doctor-diagnosed RA and validated by medical record review, as reported previously [2,11,15]. Definite RA was defined based on the 1987 American College of Rheumatology criteria and two expert rheumatologist reviewers' agreement. We included cases with first RA symptoms $\geq$ 3 months after blood draw. Seropositive RA included rheumatoid factor or anticitrullinated peptide (anti-CCP) positivity from medical records, and/or anti-CCP2 positivity at blood draw (described below).

Identification of matched controls

We identified three controls per RA case from subjects with stored blood, matched on year of birth, race, menopausal status/postmenopausal hormone use, time of day, fasting status and menstrual phase (among premenopausal women). Unconfirmed RA and other connective tissue diseases were excluded.

Laboratory methods

Plasma MCP-1 was measured by ELISA (R&D Systems, MN, USA, Boston Children's Hospital, MA, USA). Assay variabilities at concentrations of 74.2, 352 and 1076 pg/ml were 6.7, 5.8 and 4.6%, respectively. Coefficients of variation (CV) for MCP-1 in NHS samples were excellent and <10%. Levels of TNFR2 and IL-6 were measured by ELISA (R&D Systems, MN, USA, Boston Children's Hospital, MA, USA) as described previously [11]. Reactivity to 18 ACPA targeted to synovial epitopes was measured in raw fluorescent intensity units and positive if greater than three standard deviations above the control mean (Stanford University) [16]. Intrabatch CVs were 4–10% and interbatch CVs were 6–16%. The number of positive reactivities was used to create a variable called 'ACPA count', which represents the amount of diversity in ACPA reactivity. Anti-CCP2 assay was performed by bead-based microarray (Bio-Rad Laboratories, CA, USA; relative fluorescence >1500 considered positive). Human leukocyte antigen-shared epitope (*HLA-SE*) alleles were determined at the American Red Cross (MA, USA) as previously described [16]. *HLA-SE* positive was defined as one or more SE allele (*HLA-DRB*0401, 0404, 0405, 0408, 0101, 0102, 1001* or **09*).

Covariates

Lifestyle exposures were collected using biennial questionnaires [2,9] and updated through the cycle before the blood draw. Smoking was measured in pack-years (smoking years $\times$ packs/day) [2]. Alcohol was assessed every 4 years with a semi-quantitative food frequency questionnaire. Total alcohol intake in mean g/day was cumulatively updated. We classified BMI as normal ($18 \text{ kg/m}^2 \leq \text{BMI} < 25 \text{ kg/m}^2$), and overweight or obese ($\text{BMI} \geq 25.0 \text{ kg/m}^2$). Less than 1% of participants had missing data for each covariate, and median values from the control group were imputed.

Statistical analysis

MCP-1 was log transformed to improve normality when used as a continuous variable. We employed Spearman correlations to assess relationships between continuous BMI, smoking and alcohol and log-MCP-1 plasma concentrations among cases and controls separately. We examined a possible departure from linearity in the relationship between log-MCP-1 and the log odds of RA by using a likelihood ratio test comparing the model with only the linear term to one with linear and nonparametric-restricted cubic spline terms. We excluded extreme observations identified using the extreme Studentized deviate many-outlier detection procedure in a sensitivity analysis.

MCP-1 was categorized into quartiles based on the distribution in controls. High MCP-1 was defined as 4th quartile (MCP-1 $\geq 524.2 \text{ pg/ml}$) [11]. The sensitivity and specificity for high MCP-1 alone and in addition to anti-CCP2, TNFR2 and IL-6 were calculated.

Multivariable conditional logistic regression models estimated odds ratios (OR) and 95% CIs for RA risk, adjusted for smoking, BMI, alcohol and menstrual regularity as these were associated with RA in these cohorts [15]. We investigated associations between MCP-1 and RA serologic phenotypes, and examined associations stratified by time (<5 years and 5 to <10 years and ≥ 10 years) and presence/absence of *HLA-SE* alleles.

We tested for multiplicative and additive interactions between high MCP-1 and smoking (0 to 10 vs >10 pack-years); BMI (<25 vs ≥25 kg/m²) and alcohol intake (0 to <5 vs ≥5 g/day). For multiplicative interactions, we included a product term in regression models and calculated a ratio of odds ratios. For additive interactions, we calculated a relative excess risk of interaction using a linear odds ratio model. We excluded women with BMI <18 kg/m² (n = 3) in a sensitivity analysis. Analyses were performed using SAS v.9.3.

Results

Among the women in the NHS who provided blood samples (n = 62,439), incident RA was confirmed in 220 women, who were matched to 675 controls. Mean age at blood draw was 52 years. The time from blood draw until RA diagnosis ranged from 4 months to 19 years, with a mean time to diagnosis of 8.5 years (Table 1). The mean age at RA diagnosis was 60.7 years and 60% of cases were seropositive.

MCP-1 ranged from 150.1 to 3871.8 pg/ml in controls and from 223.1 to 1603.9 pg/ml in cases. The median MCP-1 concentration was 442.2 pg/ml in controls and 475.2 in cases (Table 1).

We observed a positive correlation between smoking and MCP-1 plasma concentration among controls (Spearman $r = 0.12$, $p = 0.002$), but not pre-RA cases. There were positive correlations between BMI and MCP-1 among cases and controls ($r = 0.18$, $p = 0.008$ and $r = 0.09$, $p = 0.02$, respectively). We did not observe correlations between alcohol intake, ACPA count, anti-CCP2 and MCP-1 concentration in cases or controls. We observed significant positive correlations between MCP-1 and IL-6 and TNFR2 in cases (IL-6, $r = 0.13$; TNFR2, $r = 0.25$) and controls (IL-6, $r = 0.23$; TNFR2, $r = 0.14$).

The sensitivity and specificity for high MCP-1 was 36.8 and 75.0%, respectively (Table 2). Within 5 years of RA diagnosis, the sensitivity increased to 43.1%. MCP-1 had a higher sensitivity than TNFR2 with similar specificity. IL-6 and MCP-1 had similar sensitivities. Accuracy did not improve when MCP-1, TNFR2 and IL-6 were combined nor when anti-CCP2 positivity was included (Table 2).

In fully adjusted models, the OR for RA among heavy smokers (>10 pack-years vs 10 pack-years or never smoking) was 1.82 (95% CI: 1.30–2.55). The OR for RA among those with BMI ≥25 was 1.39 (95% CI: 1.01–1.90). Cumulative alcohol intake was not associated with RA risk (OR: 1.19; 95% CI: 0.84–1.69), although in the parent NHS/NHSII cohorts we observed a protective effect of moderate alcohol [4].

MCP-1 concentration was statistically significantly associated with increased RA risk and the relationship appeared to be linear. A one-unit increase in log-MCP-1 was associated with a twofold increase in RA risk (OR: 1.95; 95% CI: 1.14–3.33). The highest quartile of MCP-1 was strongly associated with both sero-negative (OR: 1.85) and seropositive (OR: 1.57) RA in adjusted models (Table 3). The association was especially strong for RA developing within 5 years (OR: 2.42). MCP-1 was more strongly associated with RA among those who were *HLA-SE* positive (OR: 2.05) than negative (OR: 1.40; p for additive interaction = 0.04). Multiplicative interaction between MCP-1 and *HLA-SE* was not

statistically significant ($p = 0.13$). Results were similar excluding nine individuals with outlying values.

Of the seropositive RA cases, 65.6% were *HLA-SE* positive compared with 44.3% of the seronegative RA cases. The fully adjusted OR for RA associated with high MCP-1 among both seropositive and *HLA-SE*-positive individuals was 1.66 (95% CI: 1.02–2.71).

Interaction analyses revealed that the associations between plasma log MCP-1 and RA did not differ by smoking, BMI or alcohol intake prior to the time of the blood draw (Table 4). In sensitivity analyses excluding women with BMI $<18 \text{ kg/m}^2$, results were unchanged.

Discussion

In this large nested case–control study of women, the chemokine MCP-1 was strongly associated with seropositive and seronegative RA. MCP-1 is a central chemokine of inflammation, produced by monocytes and macrophages in the inflammatory response in particular, but also by adipocytes in obesity. It is produced in response to inflammatory cytokines, such as TNF- α and IL-1. We observed that MCP-1 was present at elevated concentration in the blood of women who developed RA several years later. While there were positive correlations between smoking, obesity and MCP-1 plasma concentration, contrary to our hypothesis, the association between MCP-1 and RA did not vary by smoking status, BMI or alcohol intake prior to the blood draw. There was a 2.4-fold increase in odds of RA associated with high MCP-1 in the 5 years before diagnosis. The ORs for RA within 5–10 years and 10 or more years were lower, but still elevated. This may point toward an increasing inflammation in the years before diagnosis that parallels the increase in ACPA positivity seen in previous studies [1]. The association was stronger among women with *HLA-SE* alleles, with an additive interaction between MCP-1 and *HLA-SE*. This finding is interesting in light of recent confirmation that *HLA-SE* alleles are associated not only with RA susceptibility, but also with RA severity, radiologic damage, treatment effect and mortality [17].

In a Swedish case–control study utilizing banked samples, MCP-1 was higher among 92 RA patients compared with controls, in particular among ACPA-positive patients, in samples drawn prior to RA [12]. However, in a study using samples from 73 military recruits in the US Department of Defense Biorepository, no significant association between MCP-1 and future RA was detected [18]. Studies of MCP-1 among first degree family members of RA patients have also had conflicting results. Among 106 first-degree relatives (FDRs) of RA patients in the Studies of the Etiology of RA (SERA), no association was observed between MCP-1 and rheumatoid factor or inflammatory cytokines [19]. However, in a native American population study, MCP-1 was markedly higher in RA FDRs than North American native controls, and indeed levels were comparable in FDRs and RA patients [20].

Our study was larger in size than previous studies and benefits from blood samples prior to RA onset. Our results may not be generalizable to women of different races due to the inclusion of mainly Caucasian women. Furthermore, our results are generalizable to older

onset RA since the average age at RA diagnosis was 60 years old. We had limited power to detect modest interactions in some subset analyses.

Past studies have reported MCP-1 concentrations to be elevated in obese compared with lean individuals [21]. With recent understanding of the metabolic activity of adipose tissue, there is a growing recognition of obesity as a proinflammatory state [22]. It is proposed that adipose tissue may be exerting its effects on the pathogenesis of RA and other diseases via inflammatory adipokines, including MCP-1 [14, 22]. MCP-1 was positively correlated with smoking and BMI, but not alcohol intake in our data. Associations between MCP-1 and RA did not vary by smoking, BMI or alcohol intake indicating that the relationship may be independent of these factors. Statistical interactions can point to, but are distinct from, biological interactions. Further dissection of these complex pathways and feedback loops is therefore required. MCP-1 was correlated with IL-6 and TNFR2 and it is still unclear whether one is more important in predicting RA than another. MCP-1 is a marker of not only inflammation, but also of cell migration toward a site of injury or infection, indicating strong inflammatory reaction and perhaps the onset of synovial inflammation in RA. Future studies should include MCP-1 in prediction models as it shows similar sensitivity and specificity for pre-RA compared with IL-6 and TNFR2.

Conclusion & future perspective

Our results add to the evidence that MCP-1 is strongly related to future seropositive and seronegative RA, in particular RA within 5 years. We observed a higher risk of RA associated with MCP-1 in the presence of *HLA-SE* alleles, which suggests these factors belong to the same biologic pathway. Future research will focus on the added value of including MCP-1 in a panel of biomarkers intended for RA risk prediction, in particular among those at high risk by virtue of family history or early symptoms.

Acknowledgments

This work was supported by the NIH (grants CA186107, CA49449, CA176726, CA67262, AR59073, AR066109, AR49880, AR52403, AR947782) and a doctoral dissertation award from the Arthritis Foundation.

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Executive summary

Background

- The chemokine monocyte chemotactic protein-1 (MCP-1) is a biomarker of systemic inflammation and has been shown to predict future rheumatoid arthritis (RA) risk in one past study. It is unknown whether the RA risk associated with MCP-1 varies according to other potentially proinflammatory and anti-inflammatory lifestyle factors.

Methods & results

- This nested case-control study examined MCP-1 plasma concentration and lifestyle factors 3 months to 19 years before RA diagnosis in cases and matched controls identified in the large, prospective Nurses' Health Study cohorts.
- Subgroup analyses revealed that MCP-1 concentration was associated with both seropositive and seronegative RA, in particular within 5 years of blood draw and human leukocyte antigen-shared epitope-positive RA. No interactions with smoking, BMI or alcohol were detected.

Conclusion

- We confirm a strong association between MCP-1 and future RA risk. The risk was highest among those with human leukocyte antigen-shared epitope alleles, suggesting that these factors belong to the same pathway.

Table 1

Characteristics of preclinical rheumatoid arthritis cases and matched controls at blood collection among women in the Nurses' Health Study Cohorts.

	RA cases (n = 220)	Matched controls (n = 675)
NHS, n (%)	148 (67)	457 (68)
NHS II, n (%)	72 (33)	218 (32)
Age at blood draw, years, mean ($\pm$ SD) [†]	52.0 ($\pm$ 7.9)	52.0 ($\pm$ 8.1)
Caucasian, n (%) [†]	218 (99)	662 (98)
Premenopausal, n (%) [†]	78 (35)	241 (36)
Irregular menses, n (%)	33 (15)	64 (9)
Pack-years smoking, mean ($\pm$ SD) [‡]	22.3 ($\pm$ 16.4)	19.8 ($\pm$ 18.3)
Greater than 10 pack-years smoking, n (%)	89 (40)	192 (28)
BMI, kg/m ² , mean ($\pm$ SD)	25.8 ($\pm$ 4.9)	25.0 ($\pm$ 4.3)
BMI $\geq$ 25 kg/m ² , n (%)	110 (50)	274 (41)
Alcohol intake, g/day, mean ($\pm$ SD)	4.1 ($\pm$ 5.4)	5.6 ($\pm$ 8.7)
Less than 5 g/day alcohol intake, n (%)	157 (71)	458 (68)
Log MCP-1, pg/ml, mean ($\pm$ SD)	6.2 ($\pm$ 0.3)	6.1 ($\pm$ 0.3)
MCP-1, pg/ml, median (IQR)	475.2 (193.2)	442.2 (153.2)
Age at RA diagnosis, years, mean ($\pm$ SD)	60.7 ($\pm$ 9.9)	–
Time from blood draw to RA diagnosis, years, mean ($\pm$ SD)	8.7 ($\pm$ 4.8)	–
Seropositive (RF and/or anti-CCP), n (%)	132 (60)	–

[†] Case-control matching factors.

[‡] Pack-years among ever-smokers only.

Anti-CCP: Anti-citrullinated peptide antibody; IQR: Interquartile range; MCP-1: Monocyte chemotactic protein-1; NHS: Nurses' Health Study; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SD: Standard deviation.

Table 2

Sensitivity and specificity of high monocyte chemotactic protein-1 in combination with high TNFRII, high IL-6 and anti-cyclic citrullinated peptide positive.

	All years		Within 5 years of diagnosis	
	Sensitivity	Specificity	Sensitivity	Specificity
MCP-1 (524.2 pg/ml)	36.8	75.0	43.1	74.1
TNFRII (2740.4 pg/ml)	25.5	75.1	17.2	85.5
IL- 6 (1.42 pg/ml)	33.2	75.3	43.1	64.8
Anti-CCP2 positive	9.1	100.0	25.9	100.0
MCP-1 and TNFRII	10.9	91.0	12.1	92.8
MCP-1 and IL-6	14.6	91.0	20.7	86.5
MCP-1 and anti-CCP2 positive	3.6	100.0	6.9	100.0
MCP-1, TNFRII and IL-6	3.5	95.6	3.5	94.3
MCP-1, TNFRII, IL-6 and anti-CCP2 positive	0.5	100.0	1.7	100.0

Anti-CCP2: Anti-cyclic citrullinated peptide 2; MCP-1: Monocyte chemotactic protein-1.

Table 3

Odds ratios for rheumatoid arthritis according to high plasma monocyte chemotactic protein-1[†] among women in the Nurses' Health Study cohorts among outcome groups stratified by serologic status, time between blood collection and rheumatoid arthritis onset, and *HLA-SE* status.

Outcome group	Case No. high MCP-1/no. low MCP-1 (total n = 220)	Controls No. high MCP-1/no. low MCP-1 (total n = 675)	Adjusting for matching factors [§] OR for RA (95% CI)	Fully adjusted [¶] OR for RA (95% CI)
Overall RA	81/139	169/506	1.78 (1.28–2.48)	1.67 (1.19–2.35)
Seronegative RA	34/54	169/506	1.72 (1.13–2.91)	1.85 (1.14–2.99)
Seropositive RA [‡]	47/85	169/506	1.77 (1.18–2.66)	1.57 (1.03–2.39)
RA within 5 years	25/33	50/143	2.27 (1.21–4.26)	2.42 (1.22–4.80)
RA within 5 to <10 years	24/49	51/169	1.67 (0.92–3.05)	1.59 (0.85–2.99)
RA within 10 years	32/57	68/194	1.66 (0.97–2.81)	1.70 (0.98–2.94)
<i>HLA-SE</i> negative [#]	31/62	96/267	1.50 (0.91–2.47)	1.40 (0.83–2.35)
<i>HLA-SE</i> positive [#]	49/74	61/201	2.18 (1.36–3.51)	2.05 (1.25–3.36)

[†] MCP-1 plasma concentration was categorized into quartiles (based on the distribution in controls) and examined as quartile 4 vs quartiles 1 through 3 in all models.

[‡] Seropositive was defined as anti-CCP or RF positive from medical record review or anti-CCP positive blood sample at the same time as MCP-1 sample taken.

[§] Adjusted for NHS or NHSII cohort, menopausal status, age at blood draw.

[¶] Additionally adjusted for irregular menses, and mutually adjusted for pack-years smoking, BMI and cumulative alcohol intake.

[#] *HLA-SE* analysis based on those with data on *HLA-SE* (216 cases and 625 controls).

HLA-SE: Human leukocyte antigen-shared epitope; MCP-1: Monocyte chemotactic protein-1; OR: Odds ratio; RA: Rheumatoid arthritis.

Table 4

Interactions between elevated plasma MCP-1 and smoking, body mass index and alcohol intake in determining the risk of rheumatoid arthritis among women in the Nurses' Health Study Cohorts.

Measures of interaction	
Interaction between smoking (>10 pack-years vs 10 pack-years) and MCP-1	
RERI [†]	0.83 (-0.72–2.38)
ROR [‡]	1.14 (0.58–2.26)
Interaction between BMI (overweight ≥25 kg/m² vs normal <25 kg/m²) and MCP-1	
RERI [†]	0.18 (-0.98–1.34)
ROR [‡]	0.97 (0.50–1.90)
Interaction between alcohol (<5 g/day vs ≥5 g/day) and MCP-1	
RERI [†]	-0.60 (-2.0–0.87)
ROR [‡]	0.65 (0.32–1.32)

MCP-1 plasma concentrations were categorized into quartiles (based on the distribution in controls) and examined as quartile 4 vs quartiles 1 through 3 in all models.

All models adjusted for NHS or NHSII cohort, menopausal status, age at blood draw, irregular menses, and mutually adjusted for pack-years smoking, BMI and cumulative alcohol intake.

[†]RERI >0 indicates additive statistical interaction.

[‡]ROR (exponentiated beta from interaction term in regression model) >1 indicates multiplicative statistical interaction.

NHS: Nurses' Health Study; NHSII: Nurses' Health Study II; RERI: Relative excess risk due to interaction; ROR: Ratios of odds ratios.