# Plasma Level of CXC-Chemokine CXCL12 Is Increased in Rheumatoid Arthritis and Is Independent of Disease Activity and Methotrexate Treatment

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*ABSTRACT*. ***Objective.*** Several actions of the chemokine CXCL12 have potential relevance for rheumatoid arthritis (RA). Interaction with CXCR4, the unique receptor for CXCL12, stimulates angiogenesis, mononuclear cell trafficking into the joints, lymphoid-tissue-like rearrangement of T cells within the synovium, and chondrocyte release of cartilage-degrading metalloproteinases. We investigated the level of CXCL12 in plasma (p-CXCL12) as a marker of RA diagnosis, RA disease activity, and response to methotrexate (MTX) treatment.

***Methods.*** A prospective study including 36 patients with RA (ACR criteria) of at least 6 months' duration, and 50 sex and age matched healthy controls. ELISA for CXCL12 was performed on plasma prior to and after 16 and 28 weeks of MTX treatment in the patients with RA and once in controls.

***Results***. The p-CXCL12 was 1855 ± 145 pg/ml in RA patients and 1273 ± 79 pg/ml in controls ($p < 0.001$). During the 28 weeks of MTX treatment, the ACR disease activity variables decreased, whereas the p-CXCL12 level remained constant and increased. P-CXCL12 was not correlated to any ACR disease activity variable at any time ($p > 0.05$).

***Conclusion.*** Patients with RA had a significantly and constantly increased p-CXCL12 level compared to controls. The p-CXCL12 level was independent of any ACR disease activity variables, as well as response to MTX treatment. (J Rheumatol 2006;33:1754–9)

*Key Indexing Terms:*
STROMAL CELL-DERIVED FACTOR-1α CXCL12 CXCR4
RHEUMATOID ARTHRITIS CHEMOKINES

Rheumatoid arthritis (RA) is a chronic, inflammatory disease, mainly affecting synovial joints. The cause of the inflammation and its primary confinement to the joints is unknown. A possible contributor is the complex system of cytokines and chemokines exhibiting regulatory actions in the inflammatory system[1-5]. Chemokines are major regulators of cell trafficking from blood to tissue[6-8]. The production and secretion of CXCL12, a CXC chemokine with many actions of potential importance for the development of RA, has been demonstrated in joint endothelial cells[9,10]. It causes migration of selected bypassing mononuclear cells[4,11-15], especially CD4+ T cells, which are the dominating cells in the joints of patients with RA[14,16]. The coupling of CXCL12 to CXCR4 further causes T cell accumulation in the synovium of RA patients through both inhibition of synovial T cell apoptosis[17-19] and active retention of T cells in the RA synovium[20]. This ligand-receptor pair also stimulates the lymphoid tissue-like rearrangement of T cells, primarily of the CD4+CD45RO+ memory type, in chronic inflammatory synovial tissue[11,20-22]. Within the joint, the fibroblast-like synoviocytes (FLS) produce and secrete CXCL12[23-25], and CXCL12-CXCR4 interaction elicits stimulation of angiogenesis[9,10,26-31], which is important for the uncontrolled growth of pannus in RA[32,33]. CXCR4, but not CXCL12, is highly expressed on chondrocytes, and coupling to CXCL12 causes release of metalloproteinases (MMP), which are cartilage matrix-degrading enzymes[34-37]. All actions of the CXCL12-CXCR4 system described here are most probably highly specific, because, unlike most other CXC chemokines, CXCL12 binds to only one receptor, CXCR4[13,38], even though there has been one report that CXCL12 also binds to CXCR7[39]. Concerning patients with RA, there are no data on an association between CXCL12 and

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disease activity. The concentration of CXCL12 in synovial fluid (SF) from patients with RA has been measured more than 10-fold higher compared to that in healthy controls and almost 3-fold higher than that in patients with osteoarthritis (OA)[40]. Recently, CXCL12 was shown to be expressed in RA synovial tissue despite a marked clinical treatment response to anti-tumor necrosis factor-α (anti-TNF-α)[41].

The aim of our study was to test if the level of CXL12 in plasma was correlated to RA per se, to disease activity, and to response to methotrexate (MTX) treatment.

## MATERIALS AND METHODS

*Patients*. The study was carried out at the Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark. Participation was based on patients' written consent according to the Declaration of Helsinki[42], and the study was approved by the local ethical committee.

Eligible for inclusion were 36 patients with RA fulfilling the American College of Rheumatology (ACR) diagnostic criteria[43]. Disease duration was > 6 months, with a mean of 13.3 years (range 0.5–45). The distribution by sex was 25 women and 11 men, with a mean age of 55.1 years (range 32–77). All 36 patients were MTX-naive, 11 patients were DMARD-naive, and 25 patients had taken disease modifying antirheumatic drugs (DMARD): one DMARD (17 patients), 2 (3 patients), or at least 3 DMARD (5 patients) including salazopyrin, myochrysine, penicillamine, auranofin, and hydroxychloroquine. These 25 patients underwent a 4-week washout period prior to start with MTX treatment. The initial dose of MTX was 7.5 mg once weekly and, with signs of disease activity at the monthly followup, the weekly dose was escalated by 2.5 mg. The mean dose of MTX for the 36 RA patients after 0, 16, and 28 weeks was 7.5, 8.5, and 9.8 mg, respectively, and a dose range of 5–15 mg. Oral prednisone was administered to 17 patients for the whole 28-week study period at a mean dose of 9.7 mg (2.5–30 mg/day). No patient received intraarticular steroid. Nonsteroidal antiinflammatory drug use was allowed.

After MTX start, disease activity was assessed in all patients by the same physician at Weeks 0, 16, and 28. The assessing physician was blinded to the physician in charge of MTX treatment and dose adjustment for disease activity, adverse events, and the study objective of disease remission. Disease activity was assessed by the swollen joint count (a modified ACR 28 index with addition of ankles and 10 metatarsophalangeal joints adding up to a total of 40 joints[44], the tender joint count (the same count with addition of the hips, thus a total of 42), physician's global assessment of disease activity on a 5-point numeric rating scale (NRS), patient's global assessment of disease activity on a 10 point NRS, patient's HAQ score (Stanford Health Assessment Questionnaire)[45] of functional activity (from 0 to 3), and finally, pain score on a 10 point NRS. Response to MTX treatment was evaluated by the ACR criteria of improvement[46,47].

Plasma samples from 50 healthy control subjects were collected; their female to male ratio was 1:1 and their mean age was 47 years (range 22–65).

*Plasma*. For several reasons, plasma, rather than synovial fluid and synovial tissue, was chosen for CXCL12 analysis. First, to potentially serve as a marker for diagnosis, disease activity, and response to MTX treatment in RA, the analyzed medium should be easily accessible, reproducible (serial measurements over 28 weeks), and part of daily clinical handling of the patients. Second, plasma samples are far more acceptable for the participants. Third, pilot studies had shown increased levels in RA patients compared to healthy controls.

Plasma from RA patients and healthy controls was isolated from heparinized blood samples after centrifugation and frozen in aliquots at –80°C for later analysis.

To check for diurnal variation in plasma-CXCL12 (p-CXCL12) a total of 29 patients with RA had 4 blood samples taken within 24 hours at time 0, 6, 12, and 24 hours.

*ELISA analysis*. CXCL12 ELISA was performed using kits from R&D Systems, Abingdon, UK (catalog no. DSA00). All samples were run in doublets and, if the coefficient of variation (CV) was > 10%, the samples were rerun.

The assay was checked for intraassay (CV = 4.5%) and interassay variation (CV = 12.5%), spike recovery, linearity (dilution), and cross-reactivity with other isotypes. All validation results were in accord with those reported by R&D Systems.

*Statistics*. Spearman's rank-order correlation analysis was applied to the relationship between p-CXCL12 and each single RA activity variable. Student's t test was used to compare p-CXCL12 in the 50 healthy controls to that of the 36 patients with RA. This test was also applied on the comparison of p-CXCL12 levels at Weeks 0, 16, and 28. P values < 0.05 were considered significant.

## RESULTS

In the 36 patients with long-standing RA, p-CXCL12 was increased compared to that in the 50 healthy controls (Figure 1; $p < 0.001$). The p-CXCL12 level remained constant over time in the RA patients (Figure 2) and showed no correlation to ACR disease activity variables before start of MTX treatment (Week 0) or after 16 and 28 weeks (Table 1, Figure 3) [correlation coefficients (r values) between 0.32 and 0.02, corresponding to p values between 0.055 and 0.912]. The plots of RA disease activity versus p-CXCL12 level after 16 and 28 weeks of MTX are not shown, but followed the same patterns as in Figure 3 and showed no significant correlation. Arbitrarily, RA patients were grouped according to p-CXCL12 levels: increase > 10% (12.3–50.9%), decrease > 10% (14.8–43.8%), constant over the 28-week study period, and compared with RA disease activity; no differences were observed ($p = 0.389–0.967$). The 36 RA patients were divided

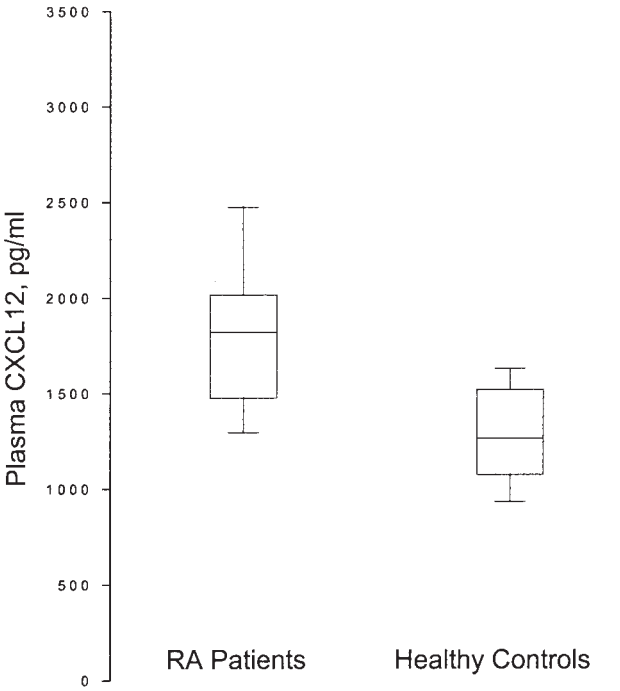


*Figure 1*. Plasma CXCL12 level in patients with RA (n = 36) and healthy controls (n = 50). Lines in boxes indicate mean values, their height representing 25th and 75th quartiles; 10th and 90th percentiles are also shown.

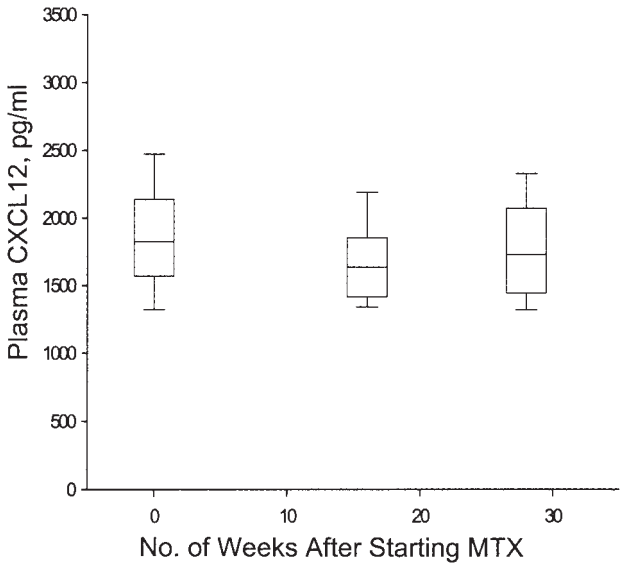


*Figure 2*. P-CXCL12 in 36 patients with long-standing RA before and 16 and 28 weeks after start with MTX treatment. Lines in boxes indicate mean values, their height representing 25th and 75th quartiles; 10th and 90th percentiles are shown.

into 3 groups of 12 each, based on the level of p-CXCL12 prior to start with MTX. From the one-third of patients with the highest p-CXCL12 values (> 2000 pg/ml, representing values exceeding 95% CI of the mean) the values for each of the ACR-defined RA activity variables were compared to the same values from the one-third of patients with the lowest p-CXCL12 values (< 1710 pg/ml, representing values below the 95% CI of the mean). No RA disease activity variable levels in these 2 groups differed from each other (p values between 0.213 and 0.546).

Concerning the response to MTX treatment, 11 patients (30%) had at least ACR20 response 28 weeks after MTX start, 19 patients (53%) were nonresponders, and 6 patients (17%) had no Week 28 response data for reasons unrelated to RA activity. Responders (> ACR20) and nonresponders to MTX treatment after 28 weeks had equal p-CXCL12 levels (p = 0.483). To test whether oral prednisone influenced the p-CXCL12 level, we compared levels in the 17 patients who were receiving prednisone to 19 patients who were not, but found equal values in the 2 groups (p = 0.949).

We found no diurnal fluctuations in the p-CXCL12 level when blood samples were taken after 0, 6, 12, and 24 hours from each of 29 patients with RA.

In summary, a high p-CXCL12 level was associated with the RA diagnosis per se. The p-CXCL12 remained high over time and was independent of disease activity including inflammatory variables and response to MTX treatment.

## DISCUSSION

This is the first prospective, clinical study concerning CXCL12 in RA. The p-CXCL12 level was significantly elevated in 36 patients with long-standing RA compared to that in 50 healthy controls. This finding indicates that the p-CXCL12 level might serve as a diagnostic marker for RA. However, the specificity of the high p-CXCL12 level in RA should be clarified by comparison to its level in patients with OA, systemic lupus erythematosus, and chronic inflammatory bowel disease, etc.

Chemokines have generally been regarded as locally acting, paracrine or autocrine proteins, and several authors have reported a high local production of CXCL12 in RA joints, considerably higher than in OA and normal joints[11,16,22,40,48]. We observed that the CXCL12 level was markedly increased in the circulation of patients with RA. Whether this represents a "spill-over" from the joints or hitherto unnoticed extraarticular production of this chemokine is not known. Simultaneous measurements of CXCL12 in both synovial biopsies and synovial fluid from affected joints and plasma could have elucidated this question. However, ethical and practical obstacles were a hindrance.

p-CXCL12 remained at a fixed high level among RA patients throughout the 28-week study period and was independent of any ACR disease activity variable, as well as response to MTX treatment. A constant and high p-CXCL12 level, uninfluenced by a decreasing disease activity and inflammatory activity over time, is in agreement with RA as a chronic, incurable condition, orchestrated by many cellular

*Table 1*. ACR disease activity variables in 36 patients with long-standing RA (> 6 mo) before starting (Week 0) and after 16 and 28 weeks of MTX therapy. Values are mean (range). Plasma CXCL12 data are given for comparison.

| | Week 0 | Week 16 | Week 28 |
|---|---|---|---|
| CRP, nmol/l | 252 | 230 | 172 |
| No. of swollen joints, maximum 40 | 6.4 (0–24) | 4.0 (0–17) | 3.7 (0–16) |
| No. of tender joints, maximum 42 | 10 (0–36) | 6.7 (0–36) | 7.1 (0–32) |
| HAQ score, 0–3 | 0.84 (0–2.38) | 0.72 (0–2.25) | 0.57 (0–1.38) |
| Physician's global activity assessment, 5 point NRS | 1.9 (0–4) | 1.3 (0–3) | 1.6 (0–3) |
| Patient's global activity assessment, 10 point NRS | 5.2 (0–9) | 3.3 (0–8.5) | 3.5 (1–8) |
| Patient's referral of pain, 10 point NRS | 2.8 (0–8) | 1.9 (0–7) | 2 (0–7.5) |
| Plasma CXCL12, mean (95% CI) | 1854 (1709–1999) | 1694 (1576–1812) | 1783 (1643–1923) |

NRS: numeric rating scale.

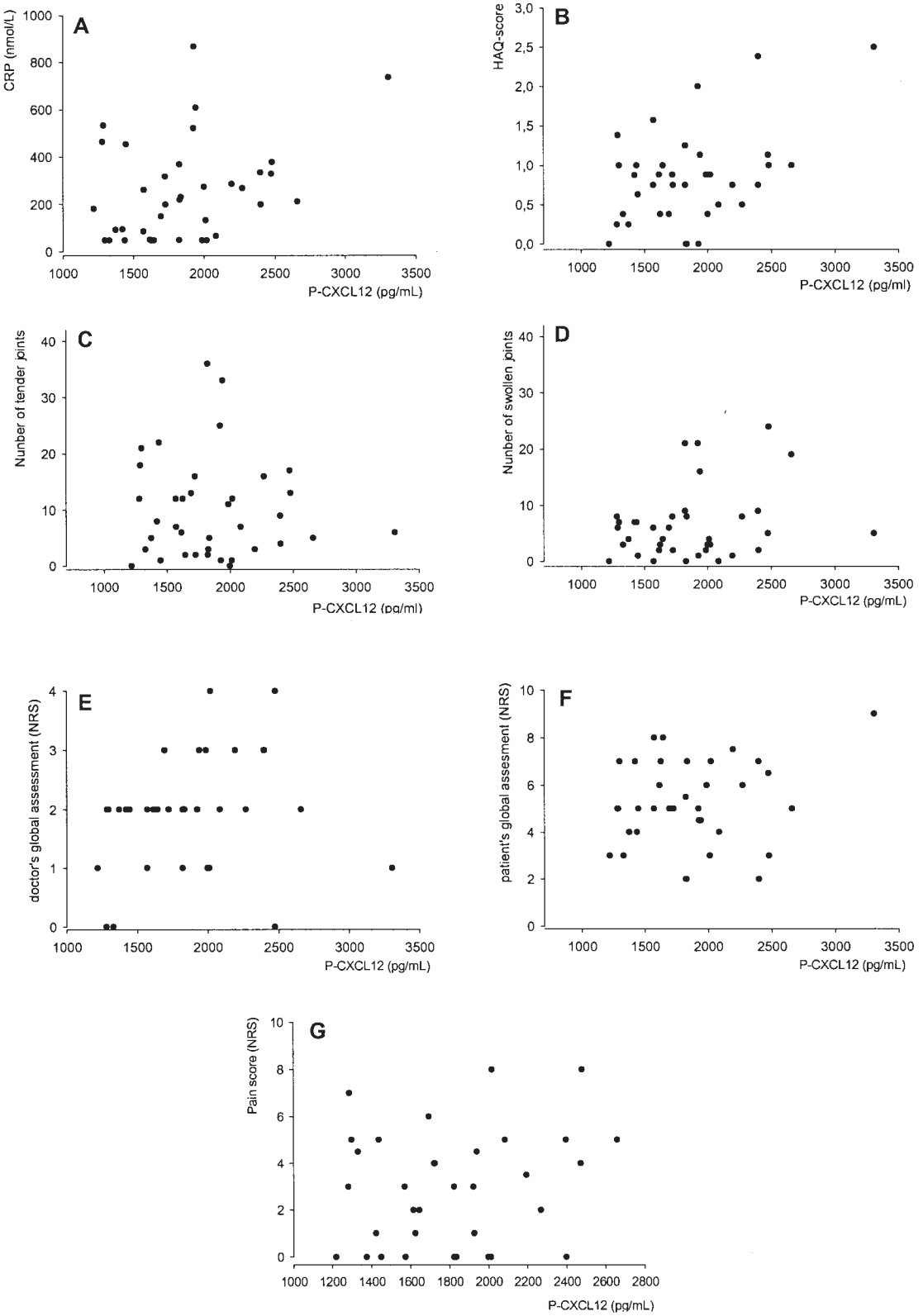


*Figure 3*. Correlation between p-CXCL12 and disease activity (ACR variables) in 36 patients with RA prior to start with MTX. A: C-reactive protein (CRP). B: Patient Health Assessment Questionnaire (HAQ). C: Number of tender joints. D: Number of swollen joints. E: Doctor's global assessment of RA activity. F: Patients' global assessment of RA activity, numeric rating scale (NRS). G: Patients' pain score. r = correlation coefficient. p = probability (Spearman's rank order). A: r = 0.29, p = 0.081. B: r = 0.14, p = 0.419. C: r = 0.02, p = 0.912. D: r = 0.32, p = 0.055. E: r = 0.28, p = 0.097. F: r = 0.09, p = 0.615. G: r = 0.12, p = 0.52.

and molecular proinflammatory activities, including production of CXCL12 from endothelial cells and FLS[6,14]. Recent data showing elevated CXCL12 in RA synovial fluid[40] and the continuous expression of CXCL12 in RA synovial tissue, irrespective of an excellent treatment response to anti-TNF-α[41], are also in good agreement with our finding of a constantly elevated p-CXCL12 level over time, independent of response to MTX.

The lack of correlation between level of p-CXCL12 and any single ACR disease activity criterion, including C-reactive protein, indicates that CXCL12 is not "just another acute phase reactant." This view gains support by the absence of significant differences between the values of RA disease activity variables from the one-third of patients with the highest p-CXCL12 and one-third of patients with the lowest p-CXCL12.

Our validation of the CXCL12 ELISA showed only small inter- and intraassay variations and therefore the variation in our measurements cannot explain our findings.

In summary, this clinical, prospective study presents evidence of increased p-CXCL12 level in patients with RA. The p-CXCL12 level was constant over time and was not associated with RA disease activity variables (ACR) or response to MTX and oral steroid treatment.


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