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CLINICAL FEATURE
ORIGINAL RESEARCH

Calprotectin levels in rheumatoid arthritis and their correlation with disease activity: a meta-analysis

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ABSTRACT

Objective: We evaluated the relationship between calprotectin levels and rheumatoid arthritis (RA), and the correlation between plasma/serum calprotectin and RA activity.

Methods: We searched PUBMED, EMBASE, and Cochrane databases and performed meta-analyses comparing plasma/serum or synovial fluid calprotectin levels in RA patients and controls, and correlation coefficients between calprotectin levels and disease activity for 28 joints (DAS28) as well as C-reactive protein (CRP) in RA patients.

Results: Sixteen studies including 849 RA patients and 266 controls were available for meta-analysis. Meta-analysis showed that calprotectin levels were significantly higher in the RA group than in the control group (SMD = 2.337, 95% CI = 1.544–3.130, $p < 1.0 \times 10^{-8}$). Stratification by rheumatoid factor (RF) status revealed significantly elevated calprotectin levels in the RF-positive RA group compared to that of the RF-negative RA group (SMD = 0.574, 95% CI = 0.345–0.804, $p = 9.2 \times 10^{-7}$). Meta-analysis of correlation coefficients identified a significant positive correlation between calprotectin levels and CRP or DAS28 (correlation coefficient for CRP = 0.566, 95% CI = 0.512–0.615, $p < 1.0 \times 10^{-8}$; correlation coefficient for DAS28 = 0.438, 95% CI = 0.269–0.518, $p = 2.5 \times 10^{-6}$). Calprotectin levels in synovial fluid were significantly higher in the RA group than in the control group (SMD = 2.891, 95% CI = 1.067–4.715, $p = 0.002$).

Conclusions: Our meta-analysis demonstrates that circulating and synovial fluid calprotectin levels are high in patients with RA, and that circulating calprotectin levels positively correlate with RA activity.

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KEYWORDS
Calprotectin; rheumatoid arthritis; activity

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that predominantly affects the synovial joints causing significant morbidity and shortened life expectancy [1]. RA is characterized by the infiltration of the synovium with neutrophils, macrophages, T cells, B cells, and dendritic cells, with subsequent tissue damage [2]. Although its cause and pathogenesis are not fully understood, it has been established that the inflammatory process plays a key role in RA in the synovial joints [2].

Calprotectin is a major monocyte/macrophage and neutrophil granulocyte protein that is released during endothelial and monocyte interaction [2]. It is also known as S100A8/S100A9, myeloid-related protein (MRP)-8/MRP-14, or calgranulin A and B. Calprotectin is an endogenous toll-like receptor-4 (TLR-4) ligand that exerts strong proinflammatory effects on phagocytes and endothelial cells to promote inflammatory processes [3]. Calprotectin was shown to be involved in joint inflammation and leucocyte infiltration in experimental antigen-induced arthritis [4], as it is secreted from activated granulocytes and monocytes/macrophages in the synovium and synovial fluid during inflammation [4]. Calprotectin is released at the local site of inflammation and plasma levels have been suggested to be a biomarker that reflects disease activity in inflammatory diseases [5]. Conventional acute-phase proteins such as C-reactive protein (CRP) is mainly produced in hepatocytes after their induction by proinflammatory interleukins released during inflammation and are nonspecific for inflammation. However, calprotectin directly induces inflammation in the inflamed RA joints rather than through systemic inflammatory activity [5]. Thus, calprotectin is likely to be a more specific marker for local disease activity.

Multibiomarker disease activity (MBDA) testing using 12 serum biomarkers provides a reliable assessment for RA. However, calprotectin was not included in the MBDA test because the assay did not meet the performance criteria required for clinical testing [6]. However, calprotectin has potential as a biomarker of activity assessment, treatment response and damage prediction. Studies on circulating or synovial fluid calprotectin levels in RA patients compared to controls and on the relationship between plasma/serum levels and RA activity have been published with different results [7–22]. The reasons for such disparity might be small sample sizes, low statistical power, and/or clinical heterogeneity [23].

Previous reviews suggest that calprotectin may be a valuable diagnostic and prognostic biomarker for RA [5,24].

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Calprotectin levels in synovial fluid are high, indicating there is substantial local production by inflamed synovium. Circulating calprotectin levels, though highly variable, are elevated in active RA and fall with effective therapy. Calprotectin levels predict future erosive damage and therapeutic responses [5]. However, there has been no meta-analysis on calprotectin level in RA. To overcome the limitations of individual studies and improve precision, we performed this meta-analysis. The present study aimed to determine plasma/serum calprotectin levels in RA patients compared to those in controls, and to evaluate its correlation with disease activity using meta-analysis.

2. Materials and methods

2.1. Identification of eligible studies and data extraction

We performed a literature search for studies that examined calprotectin levels in RA patients and controls, and the relationship between plasma/serum calprotectin D levels and RA activity. PUBMED, EMBASE, and Cochrane databases were searched to identify all available articles (up to June 2016). The following key words and subject terms were used in the search: 'calprotectin,' 'level,' 'rheumatoid arthritis,' and 'RA.' All references cited were also reviewed to identify additional studies not indexed by the electronic databases. Studies were considered eligible if they adhered to any of the following criteria: (1) they were case-control, cross-sectional, or longitudinal studies with patients with RA diagnosed according to ARA 1958, ACR 1987, or ACR/EULAR classification criteria; (2) they provided data on plasma/serum and/or synovial fluid calprotectin levels in case and control groups; (3) they provided data on the correlation coefficient between circulating calprotectin levels and RA activity based on disease activity scores for 28 joints (DAS28) or CRP. We excluded studies with either of the following characteristics: (1) they contained overlapping or insufficient data; (2) they were reviews or case reports. The following information was extracted from each study: the first author, year of publication, country, study region, number of participants, study design, sample type, rheumatoid factor (RF) status, mean and standard deviation (SD) of calprotectin levels, and correlation coefficients between the calprotectin level and CRP or DAS28. When the data were presented in terms of median, or range, we computed the mean and SD using previously described formulae [25,26]. Data from the methods and results were extracted from original studies by two independent reviewers. Discrepancies between reviewers were resolved by consensus. The meta-analysis was conducted in accordance with PRISMA guidelines [27].

2.2. Evaluation of statistical associations

We performed meta-analyses examining the relationship between circulating and/or synovial fluid calprotectin levels and RA, and the correlation coefficient between circulating calprotectin level and CRP or DAS28. For data continuity, results were presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). SMDs were calculated by dividing the mean difference between the two groups by the pooled SD, and were used when different scales were integrated to measure the same concept. This measure compares case and control arms in terms of standardized scores. The magnitude of the SMD was considered as follows: 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥ 0.8, large effect [28]. We assessed within- and between-study variations and heterogeneities using Cochran's Q-statistics [29]. When the significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, the random effects model was used for meta-analysis [30]; otherwise, the fixed effects model was used. The fixed effects model assumes that all studies estimate the same underlying effect and considers only within-study variation [29]. We quantified the effect of heterogeneity using the I^2 value, where I^2 measures the degree of inconsistency between datasets [31]. Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ).

2.3. Evaluation of heterogeneity, sensitivity test, and meta-regression

To examine potential sources of heterogeneity in the meta-analysis, subgroup analysis was performed using the following variables: study region, study design, sample type, and RF status. A sensitivity test was performed to assess the influence of each individual study on the pooled odds ratio by omitting each study individually and deleting the studies with imputed data [11] or a control group of OA [20,21]. To examine possible heterogeneities in the meta-analysis, a meta-regression analysis was performed using the following variables: study region, study design, sample type, publication year, and sample size.

3. Results

3.1. Studies included in the meta-analysis

We identified 255 studies using electronic and manual searching methods, and 16 of those were selected for full-text review based on the title and abstract. Four of these were excluded, because they had duplicate data or were reviews. Thus, 16 articles met the inclusion criteria [7–22], and these consisted of 849 patients and 266 controls (Table 1). Eight of these studies examined the circulating calprotectin levels in RA and control groups; 11 and six studies provided correlation coefficients between calprotectin levels and CRP or DAS28, respectively, and four examined calprotectin levels in synovial fluid in the RA and control groups. Table 1 shows the characteristic features of studies included in this meta-analysis.

3.2. Meta-analysis of circulating calprotectin levels in RA patients compared to controls

Calprotectin levels were significantly higher in the RA group than in the control group (SMD = 2337, 95% CI = 1.544–3.130, $p < 1.0 \times 10^{-8}$) (Table 2, Figure 1). In addition, stratification by study region showed significantly elevated calprotectin levels in

Table 1. Characteristics of individual studies included in the meta-analysis.

			Number of patients		Data (calprotectin, μg/l, mean or median)							Correlation coefficient	
					Blood				Synovial fluid				
Authors	Country	Study type	RA	Control	Sample type	RA	Control	RF+	RF-	RA	OA	CRP	DAS28
Acar, 2016 [7]	Turkey	CC	28	28	Plasma	359.2	274.0	(-)	(-)	(-)	(-)	0.42	(-)
Choi, 2015 [8]	UK	L	170	(-)	Serum	(-)	(-)	(-)	(-)	(-)	(-)	0.51	0.20
Gracia-Arias, 2013 [9]	Spain	CS	60	(-)	Serum	(-)	(-)	5200	4140	(-)	(-)	0.37	0.27
Cerezo, 2011 [10]	Czech	L	43	32	Serum	5990	1920	(-)	(-)	(-)	(-)	0.55	0.47
Chen, 2009 [11]	Australia	CC	138	44	Serum	4.3[a]	1.9[a]	(-)	(-)	(-)	(-)	(-)	(-)
De Seny, 2008 [12]	Belgium	CS	34	36	Plasma	607	272	(-)	(-)	(-)	(-)	0.54	0.48
Hammer, 2007 [13]	Norway	CS	145	(-)	Plasma	(-)	(-)	2500	900	(-)	(-)	0.57	0.55
Sunahori, 2006 [14]	Japan	CS	17	17	Serum	(-)	(-)	(-)	(-)	54,800	7300	0.80	(-)
De Rycke, 2005 [15]	Germany	CS	40	20	Serum	1075	280	(-)	(-)	(-)	(-)	0.74	(-)
Drynda, 2004 [16]	Germany	CS	23	23	Plasma	14.4	1.5	(-)	(-)	475,000	970	(-)	(-)
Madland, 2002 [17]	Norway	L	56	(-)	Plasma	(-)	(-)	(-)	(-)	(-)	(-)	0.67	(-)
Burmeister, 1995 [18]	Switzerland	CS	11	17	(-)	(-)	(-)	(-)	(-)	1,739,081	28,887	(-)	(-)
Brun, 1994 [19]	Norway	CS	68	(-)	(-)	(-)	(-)	9495.7	6719.5	(-)	(-)	(-)	(-)
Brun, 1992 [20]	Norway	CS	43	43	Plasma	12,185	697[b]	(-)	(-)	(-)	(-)	0.58	(-)
Berntzen, 1991 [21]	Norway	CS	41	6	Plasma	9400	630[b]	(-)	(-)	18,156	895	0.64	(-)
Berntzen, 1988 [22]	Norway	CS	57	(-)	(-)	(-)	(-)	3037	2149	(-)	(-)	(-)	(-)

RA: rheumatoid arthritis; RF: rheumatoid factor; OA: osteoarthritis; CRP: C-reactive protein; DAS28: Disease Activity Score for 28 joints; UK: United Kingdom; CC: case control; CS: cross-sectional; L: longitudinal.
[a]Data from figure.
[b]OA as a control group, (-): not available

Table 2. Meta-analysis of calprotectin levels in RA patients compared to that in controls.

			Test of association			Test of heterogeneity		
Groups	Population	No. of studies	SMD[a]	95% CI	*p*-Value	Model	*p*-Value	I^2
All	Overall	8	2.337	1.544–3.130	$<1.0 \times 10^{-8}$	R	0.000	92.4
Region	European	6	2.802	1.728–3.875	3.1×10^{-7}	R	0.000	92.6
	Asian	1	1.604	1.227–1.982	$<1.0 \times 10^{-8}$	NA	NA	NA
	Middle Eastern	1	0.739	0.197–1.280	0.007	NA	NA	NA
Study design	Cross-sectional	5	2.517	1.458–3.577	3.2×10^{-6}	R	0.000	91.2
	Case-control	2	1.194	0.347–2.041	0.006	R	0.010	84.8
	Longitudinal	1	4.036	3.244–4.827	$<1.0 \times 10^{-8}$	NA	NA	NA
Sample type	Plasma	5	2.398	1.244–3.583	7.2×10^{-5}	R	0.000	93.2
	Serum	3	2.327	1.000–3.654	0.001	R	0.000	93.8
RF status	RF+ vs. RF-	4	0.574	0.345–0.804	9.2×10^{-7}	F	0.427	0
Synovial fluid	RA vs. OA	4	2.891	1.067–4.715	0.002	R	0.000	92.9

RA: rheumatoid arthritis; RF: rheumatoid factor, ;: fixed-effects model; R: random-effects model; NA: not applicable.
[a]Magnitude of Cohen's d effect size (SMD): 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥ 0.8, large effect

RA groups from European, Asian, and Middle Eastern populations (SMD = 2.802, 95% CI = 1.728–3.875, $p = 3.1 \times 10^{-7}$, SMD = 1.604, 95% CI = 1.227–1.982, $p < 1.0 \times 10^{-8}$, SMD = 0.739, 95% CI = 0.197–1.280, $p = 0.007$, respectively) (Table 2, Figure 1).

3.3. Meta-analysis of circulating calprotectin levels in RA patients compared to controls based on subgroup

Meta-analysis was performed on RA patients in each subgroup based on study design, sample type, and RF status. Calprotectin level was significantly higher in the RA group than in the control group in cross-sectional, case-control, and longitudinal studies (SMD = 2.517, 95% CI = 1.458–3.577, $p = 3.2 \times 10^{-6}$, SMD = 1.194, 95% CI = 0.347–2.041, $p = 0.006$, SMD = 4036, 95% CI = 3.244–4.827, $p < 1.0 \times 10^{-8}$, respectively) (Table 2). Subgroup analysis by sample type showed significantly increased calprotectin levels in the RA group in both plasma and serum groups (Table 2). Stratification by RF status revealed significantly increased calprotectin levels in the RF-positive RA group compared to the RF-negative RA group (SMD = 0.574, 95% CI = 0.345–0.804, $p = 9.2 \times 10^{-7}$) (Table 2).

3.4. Meta-analysis of the correlation between circulating calprotectin levels and RA activity

Meta-analysis of correlation coefficients showed a significant positive correlation between calprotectin levels and CRP or DAS28 (correlation coefficient of CRP = 0.566, 95% CI = 0.512–0.615, $p < 1.0 \times 10^{-8}$; correlation coefficient of DAS28 = 0.438, 95% CI = 0.269–0.518, $p = 2.5 \times 10^{-6}$) (Table 3, Figure 2). Meta-analysis revealed that calprotectin levels were positively associated with RA activity based on CRP and DAS28.

3.5. Meta-analysis of calprotectin levels in synovial fluid of RA patients compared to controls

Calprotectin levels in synovial fluid was significantly higher in the RA group than in the control group (SMD = 2.891, 95% CI = 1.067–4.715, $p = 0.002$) (Table 2).

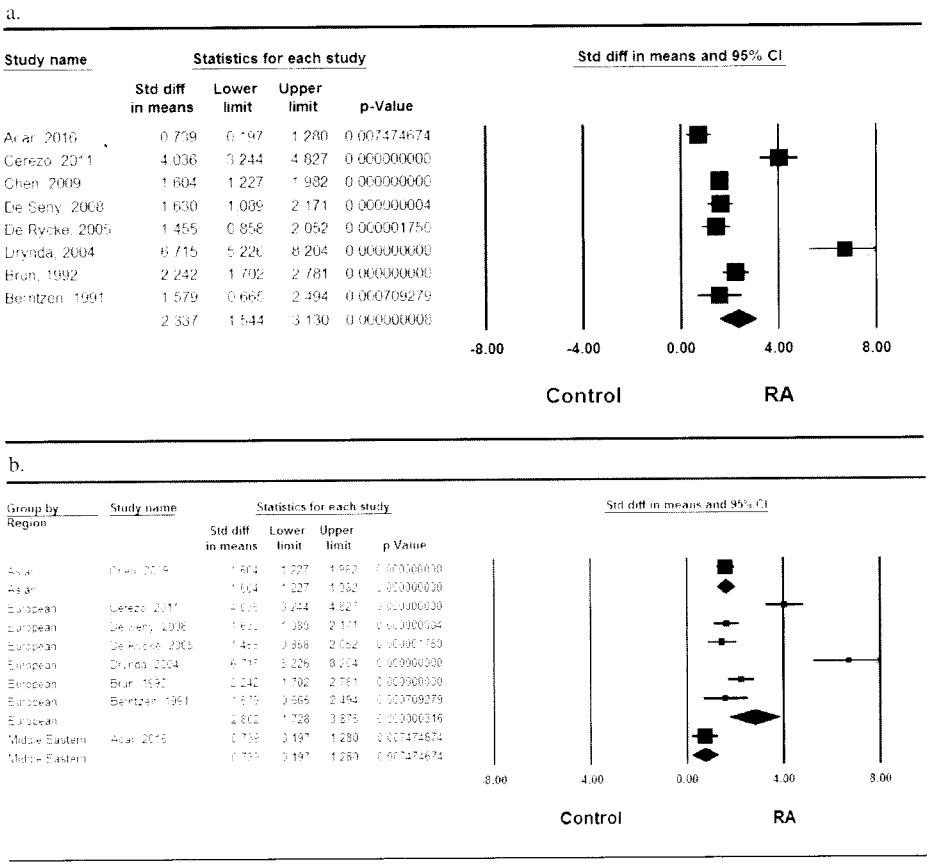

Figure 1. Meta-analysis of the relationship between plasma/serum calprotectin levels and rheumatoid arthritis in all study subjects (a) and in each region (b).

Table 3. Meta-analysis of the correlation coefficient between calprotectin level and RA activity (CRP, DAS28).

		Test of association			Test of heterogeneity		
Comparison	No. of studies	Correlation coefficient	95% CI	*p*-value	Model	*p*-value	I^2
CRP	11	0.566	0.512–0.615	$<1.0 \times 10^{-8}$	F	0.160	30.0
DAS28	6	0.438	0.269–0.581	2.5×10^{-6}	R	0.001	75.3

CI: confidence interval; R: random-effects model; CRP: C-reactive protein; DAS: Disease Activity Score

3.6. Evaluation of heterogeneity, meta-regression, and sensitivity test

Between-study heterogeneity was identified during the meta-analyses of calprotectin levels in RA patients (Table 2). The total heterogeneity was very large in the meta-analysis (I^2 = 92.4%). However, sensitivity analysis showed that no individual study significantly affected the pooled OR, indicating that the results of this meta-analysis are robust (Figure 3). The meta-regression analysis showed that study region ($p < 0.001$), study design ($p = 0.004$), publication year ($p = 0.020$), but not sample type and sample size ($p > 0.05$), had a significant impact on heterogeneity in the meta-analysis of calprotectin levels. However, the heterogeneity of each group after stratified was still very large except the RF status. The heterogeneity may be partly explained by heterogeneity in the magnitude but not direction of effect sizes observed in the subgroups. SMDs were same positive direction in all of the studies, whereas there was a difference in magnitudes of SMDs among individual studies (Figure 1). Other unknown factors affecting heterogeneity also may contribute to the difference in the relationship between calprotectin level and RA.

4. Discussion

In this meta-analysis, we combined the evidence for calprotectin status in RA with the correlation between plasma/serum calprotectin levels and RA activity. This meta-analysis of 16 studies involving 849 RA patients and 266 controls showed that circulating calprotectin levels were significantly higher in the RA group than in the control group. Calprotectin had a positive correlation with RA activity measured by DAS28 and CRP levels. Calprotectin levels were significantly elevated in the RF-positive RA group compared to that in the RF-negative RA group. In addition, calprotectin levels in the synovial fluid were significantly higher in the RA group than in the control group. The meta-analysis data suggested that calprotectin levels reflected significantly increased disease activity and

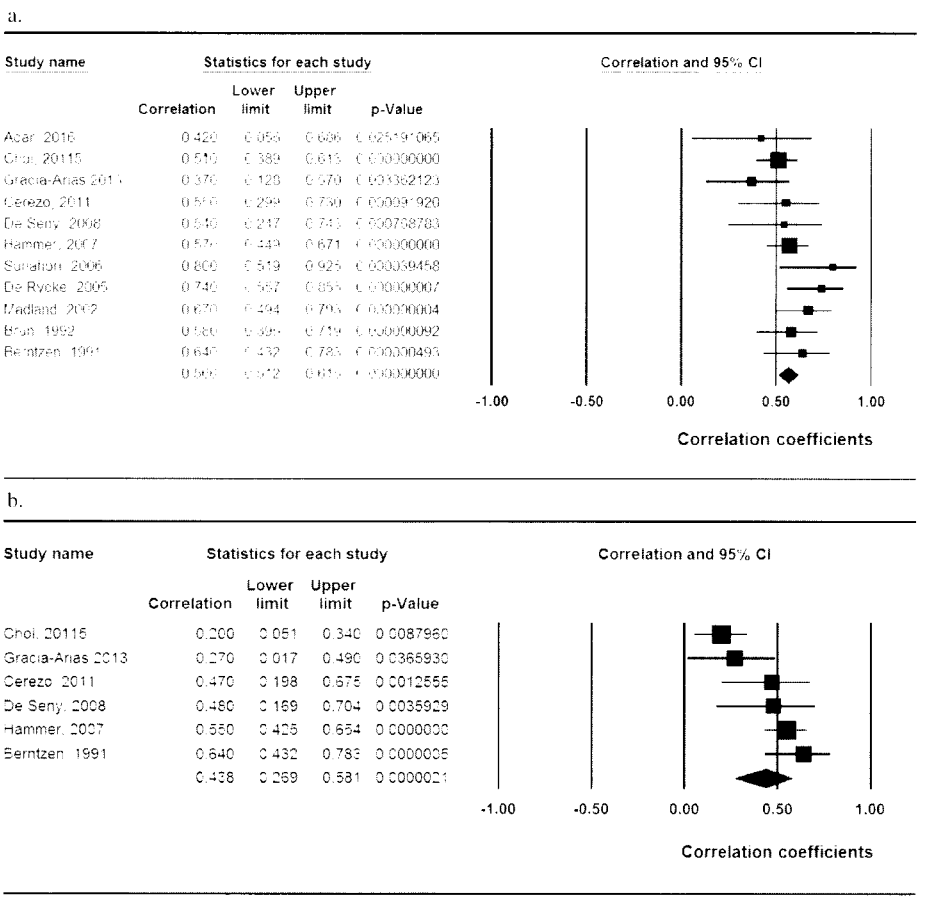

Figure 2. Meta-analysis of the correlation coefficient between calprotectin levels and CRP (a), and DAS28 (b)

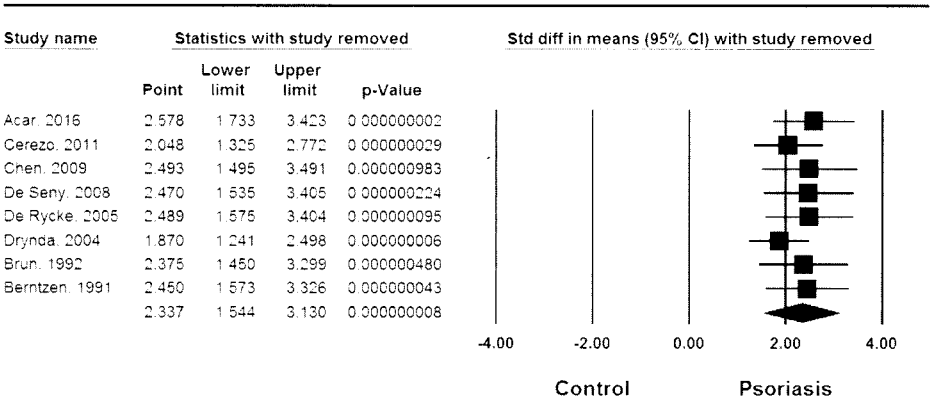

Figure 3. Sensitivity test of studies that examined the association between calprotectin levels and RA.

that calprotectin plays an important role in the proinflammatory process in RA.

Calprotectin is a major leukocyte protein of a heterodimeric complex (S100A8/A9) secreted by activated leukocytes, and binds to TLR-4, which mediates downstream signaling and promotes inflammation [3]. Extracellular calprotectin enhances the transendothelial migration of these inflammatory cells. Calprotectin is present at high concentrations in the cytoplasm of neutrophils and monocytes, and calprotectin is translocated to the membrane and cytoskeletal structures upon activation [4]. Intracellular calprotectin plays an important role in myeloid cell maturation, cell trafficking, and arachidonic acid metabolism [14]. The released calprotectin might play a role in the propagation of inflammation by recruiting neutrophils and monocytes to joints in patients with RA [14]. Calprotectin is highly expressed by synovial macrophages, and might play a role in amplifying proinflammatory cytokine responses in RA [14].

Plasma/serum and synovial fluid levels of calprotectin were markedly higher in patients with RA than in healthy controls or patients with OA. Circulating calprotectin levels are

significantly correlated with clinical and laboratory assessments of joint inflammation in RA patients, such as CRP, and DAS28. Calprotectin levels in the synovial fluid in RA were high, indicating that it is produced locally by the inflamed synovium. Because calprotectin is a small-molecular-weight protein of only 36.5 kDa, it can easily diffuse into the blood circulation from the inflamed joints [13]. Therefore, calprotectin might well reflect the severity of inflammatory activity in the RA joints, and thus has the potential to be a biomarker of inflammation for RA. Our meta-analysis revealed a significant association between calprotectin levels and RF status. This finding could be explained by the fact that RF levels provide different clinical and pathophysiological information, with RF levels being influenced by RA activity and severity [32]. Potential interference with RF may be problematic in association analysis between calprotectin and RF positive disease. The measurement of RF has changed over time. The first paper by Berntzen et al. [22] does not record how seropositivity was measured; the second paper by Garcia-Arias et al. [9], measured RF by nephelometry, which was not widely undertaken in the 1980s. Different ways of measuring RF can influence patient classification, and this has not been taken into account. Thus, combing the data has challenges. Calprotectin correlated significantly with levels of anti-cyclic citrullinated peptide antibodies (anti-CCP) in a longitudinal study of patients with very early RA [33], and multiple regression analyses showed that calprotectin was associated with anti-CCP [33]. Patients-positive anti-CCP had higher calprotectin levels at baseline and at follow-up than patients who are negative for anti-CCP [34]. However, the number of studies on relationship between calprotectin and anti-CCP was too small to perform meta-analysis.

Serum calprotectin levels may help stratify disease activity in RA patients receiving biologics [35,36]. Calprotectin levels may more accurately discriminate disease activity in RA patients treated with TNF inhibitors (TNFi.) than the acute-phase response (CRP level and erythrocyte sedimentation rate) [35]. Calprotectin also discriminates more accurately the disease status of RA patients receiving tocilizumab than acute-phase reactants [36], suggesting that calprotectin may be considered an accurate biomarker for the assessment of disease activity in RA patients receiving biologics. Serum levels of calprotectin are significantly associated with US synovitis [37,38], and predicted treatment response [38]. Calprotectin showed a potential to distinguish subclinical disease activity from deep remission (US-defined remission) in RA patients [39]. Calprotectin can predict long-term radiographic progression [34] and has potential for using calprotectin in personalizing treatment in RA [8,38].

The MBDA score was calculated using 12 biomarkers (CRP, leptin, resistin, SAA, IL-6, TNF-RI, VEGF-A, MMP-1, YKL-40, MMP-3, EGF, and VCAM-1) [40]. Calprotectin was not included in the MBDA test for technical reasons [6]. Thus, it is not widely used due to methodological issues in the assay. Analytical performance of an assay is importance in RA, because presence of heterophilic antibodies such as RF may interfere with the identification antibodies of immunoassays [41]. And heterophilic antibodies may develop as a result of treatment with biologics [41]. Improved measurement methods might lead to increased use of calprotectin as an objective biomarker for RA [40].

The present study has some shortcomings that should be considered. First, most of the studies included in this meta-analysis had small sample sizes; thus, many of the individual studies that comprise this meta-analysis may be underpowered. Second, the studies included were heterogeneous in demographic characteristics and clinical features. The heterogeneity and confounding factors such as smoking, obesity, disease activity, and drugs used, may have affected our results. Such limited data did not allow further analysis, although we performed a sensitivity test and a subgroup analysis using available confounding factors.

Nevertheless, this meta-analysis also has its strengths. Our meta-analysis is the first meta-analysis that provides combined evidence for calprotectin levels in RA patients. Individual studies included population sizes ranging from only 11 to 170, but our pooled analysis had 849 patients. Compared to individual studies, our study was able to provide data with increased accuracy regarding the relationship between calprotectin levels and RA by increasing the statistical power and resolution, through pooling the results of independent analyses.

5. Conclusion

Our meta-analysis demonstrates that circulating and synovial fluid calprotectin levels are high in RA, and that plasma/serum calprotectin levels are high in RF-positive RA patients compared to RF-negative RA patients. In addition, the circulating calprotectin levels positively correlated with RA activity. Our meta-analysis indicates that calprotectin plays a key role in the inflammation and activity of RA. Further studies are necessary to elucidate how calprotectin status directly contributes to the pathogenesis of RA.

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Declaration of interest

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References

1. Harris ED Jr. Rheumatoid arthritis. Pathophysiology and implications for therapy. N Engl J Med. 1990;322:1277–1289.
2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365:2205–2219.
3. Ehrchen JM, Sunderkotter C, Foell D, et al. The endogenous Toll-like receptor 4 agonist S100A8/S100A9 (calprotectin) as innate amplifier of infection, autoimmunity, and cancer. J Leukoc Biol. 2009;86:557–566.
4. Perera C, McNeil HP, Geczy CL. S100 Calgranulins in inflammatory arthritis. Immunol Cell Biol. 2010;88:41–49.

5. Abildtrup M, Kingsley GH, Scott DL. Calprotectin as a biomarker for rheumatoid arthritis: a systematic review. J Rheumatol. 2015;42:760–770.
6. Centola M, Cavet G, Shen Y, et al. Development of a multi-biomarker disease activity test for rheumatoid arthritis. PLoS One. 2013;8:e60635.
7. Acar A, Guzel S, Sarifakioglu B, et al. Calprotectin levels in patients with rheumatoid arthritis to assess and association with exercise treatment. Clin Rheumatol. 2016;35:2685–2692.
8. Choi IY, Gerlag DM, Herenius MJ, et al. MRP8/14 serum levels as a strong predictor of response to biological treatments in patients with rheumatoid arthritis. Ann Rheum Dis. 2015;74:499–505.
9. Garcia-Arias M, Pascual-Salcedo D, Ramiro S, et al. Calprotectin in rheumatoid arthritis: association with disease activity in a cross-sectional and a longitudinal cohort. Mol Diagn Ther. 2013;17:49–56.
10. Andrés Cerezo L, Mann H, Pecha O, et al. Decreases in serum levels of S100A8/9 (calprotectin) correlate with improvements in total swollen joint count in patients with recent-onset rheumatoid arthritis. Arthritis Res Ther. 2011;13:R122.
11. Chen YS, Yan W, Geczy CL, et al. Serum levels of soluble receptor for advanced glycation end products and of S100 proteins are associated with inflammatory, autoantibody, and classical risk markers of joint and vascular damage in rheumatoid arthritis. Arthritis Res Ther. 2009;11:R39.
12. De Seny D, Fillet M, Ribbens C, et al. Monomeric calgranulins measured by SELDI-TOF mass spectrometry and calprotectin measured by ELISA as biomarkers in arthritis. Clin Chem. 2008;54:1066–1075.
13. Hammer HB, Odegard S, Fagerhol MK, et al. Calprotectin (a major leucocyte protein) is strongly and independently correlated with joint inflammation and damage in rheumatoid arthritis. Ann Rheum Dis. 2007;66:1093–1097.
14. Sunahori K, Yamamura M, Yamana J, et al. The S100A8/A9 heterodimer amplifies proinflammatory cytokine production by macrophages via activation of nuclear factor kappa B and p38 mitogen-activated protein kinase in rheumatoid arthritis. Arthritis Res Ther. 2006;8:R69.
15. De Rycke L, Baeten D, Foell D, et al. Differential expression and response to anti-TNFalpha treatment of infiltrating versus resident tissue macrophage subsets in autoimmune arthritis. J Pathol. 2005;206:17–27.
16. Drynda S, Ringel B, Kekow M, et al. Proteome analysis reveals disease-associated marker proteins to differentiate RA patients from other inflammatory joint diseases with the potential to monitor anti-TNFalpha therapy. Pathol Res Pract. 2004;200:165–171.
17. Madland TM, Hordvik M, Haga HJ, et al. Leukocyte protein calprotectin and outcome in rheumatoid arthritis. A longitudinal study. Scand J Rheumatol. 2002;31:351–354.
18. Burmeister G, Gallacchi G. A selective method for determining MRP8 and MRP14 homocomplexes and heterocomplexes by sandwich ELISA for the discrimination of active and non-active osteoarthritis from rheumatoid arthritis in sera and synovial fluids. Inflammopharmacology. 1995;3:221–230.
19. Brun JG, Jonsson R, Haga HJ. Measurement of plasma calprotectin as an indicator of arthritis and disease activity in patients with inflammatory rheumatic diseases. J Rheumatol. 1994;21:733–738.
20. Brun JG, Haga HJ, Bøe E, et al. Calprotectin in patients with rheumatoid arthritis: relation to clinical and laboratory variables of disease activity. J Rheumatol. 1992;19:859–862.
21. Berntzen HB, Fagerhol MK, Ostensen M, et al. The L1 protein as a new indicator of inflammatory activity in patients with juvenile rheumatoid arthritis. J Rheumatol. 1991;18:133–138.
22. Berntzen HB, Munthe E, Fagerhol MK. The major leukocyte protein L1 as an indicator of inflammatory joint disease. Scand J Rheumatol Suppl. 1988;76:251–256.
23. Song GG, Lee YH. Comparison of disease activity score 28 using C-reactive protein and disease activity score 28 using erythrocyte sedimentation rate in assessing activity and treatment response in rheumatoid arthritis: a meta-analysis. J Rheum Dis. 2016;23:241–249.
24. Kang KY, Woo JW, Park SH. S100A8/A9 as a biomarker for synovial inflammation and joint damage in patients with rheumatoid arthritis. Korean J Intern Med. 2014;29:12–19.
25. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
26. Ridout KK, Ridout SJ, Price LH, et al. Depression and telomere length: A meta-analysis. J Affect Disord. 2016;191:237–247.
27. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
28. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale (NJ): L. Erlbaum Associates; 1988.
29. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ. 1997;315:1533–1537.
30. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–188.
31. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–1558.
32. Agrawal S, Misra R, Aggarwal A. Autoantibodies in rheumatoid arthritis: association with severity of disease in established RA. Clin Rheumatol. 2007;26:201–204.
33. Hammer HB, Haavardsholm EA, Kvien TK. Calprotectin (a major leucocyte protein) is associated with the levels of anti-CCP and rheumatoid factor in a longitudinal study of patients with very early rheumatoid arthritis. Scand J Rheumatol. 2008;37:179–182.
34. Hammer HB, Odegard S, Syversen SW, et al. Calprotectin (a major S100 leucocyte protein) predicts 10-year radiographic progression in patients with rheumatoid arthritis. Ann Rheum Dis. 2010;69:150–154.
35. Inciarte-Mundo J, Victoria Hernández M, Ruiz-Esquide V, et al. Serum Calprotectin Versus Acute-Phase Reactants in the Discrimination of Inflammatory Disease Activity in Rheumatoid Arthritis Patients Receiving Tumor Necrosis Factor Inhibitors. Arthritis care & research. 2016;68:899–906.
36. Inciarte-Mundo J, Ruiz-Esquide V, Hernández MV, et al. Calprotectin more accurately discriminates the disease status of rheumatoid arthritis patients receiving tocilizumab than acute phase reactants. Rheumatology. 2015;54:2239–2243.
37. Hurnakova J, Zavada J, Hanova P, et al. Serum calprotectin (S100A8/9): an independent predictor of ultrasound synovitis in patients with rheumatoid arthritis. Arthritis Res Ther. 2015;17:252.
38. Nordal HH, Brokstad KA, Solheim M, et al. Calprotectin (S100A8/A9) has the strongest association with ultrasound-detected synovitis and predicts response to biologic treatment: results from a longitudinal study of patients with established rheumatoid arthritis. Arthritis Res Ther. 2017;19:3.
39. Hurnakova J, Hulejova H, Zavada J, et al. Serum Calprotectin Discriminates Subclinical Disease Activity from Ultrasound-Defined Remission in Patients with Rheumatoid Arthritis in Clinical Remission. PLoS One. 2016;11:e0165498.
40. Bakker MF, Cavet G, Jacobs JW, et al. Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. Ann Rheum Dis. 2012;71:1692–1697.
41. Selby C. Interference in immunoassay. Ann Clin Biochem. 1999;36:704–721.