

Circulating calprotectin

A promising biomarker of inflammation

by Dr Jacqueline Gosink

Calprotectin is released during inflammatory responses and reflects local immune activation. While traditionally used to assess gastrointestinal conditions, it is showing increasing promise for evaluation of the inflammatory status in systemic autoimmune rheumatic diseases (SARDs). Enzyme-linked immunosorbent assay and chemiluminescence immunoassay technologies enable standardized measurement of circulating calprotectin and may support assessment of disease activity in SARD patients.

Calprotectin biology

Calprotectin is a calcium-binding heterodimeric protein that plays an important role in innate immune responses. It is composed of the two proteins S100A8 and S100A9 which are produced and released by activated neutrophils, monocytes and macrophages [1].

Extracellular calprotectin exerts anti-microbial activity through chelation of essential transition metals such as zinc and manganese, a mechanism known as nutritional immunity [1,3]. In addition, calprotectin promotes immune activation by stimulating the release of pro-inflammatory cytokines and enhancing leukocyte recruitment [1–3].

Under conditions of disrupted immune homeostasis, calprotectin contributes to sterile inflammation. It acts as a damage-associated molecular pattern (DAMP), activating inflammatory signalling pathways, including Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE). These pathways promote sustained cytokine production and immune cell recruitment, contributing to chronic inflammatory processes such as those observed in systemic autoimmune rheumatic diseases (SARDs) [1–3].

Biomarker in stool and blood

Calprotectin is typically elevated in inflammatory states and is a useful clinical biomarker of inflammation. Fecal calprotectin (FCALP) is an established diagnostic tool for inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis. Measurement of FCALP supports the differentiation of IBD from functional bowel diseases and is also used to monitor disease activity and progression [3].

Circulating calprotectin (cCALP) is an emerging biomarker for assessing inflammation in SARDs. Growing evidence suggests its utility in longitudinal disease monitoring, including assessment of disease activity, evaluation of treatment responses and prediction of relapses across multiple conditions [1,2].

Advantages of cCALP determination

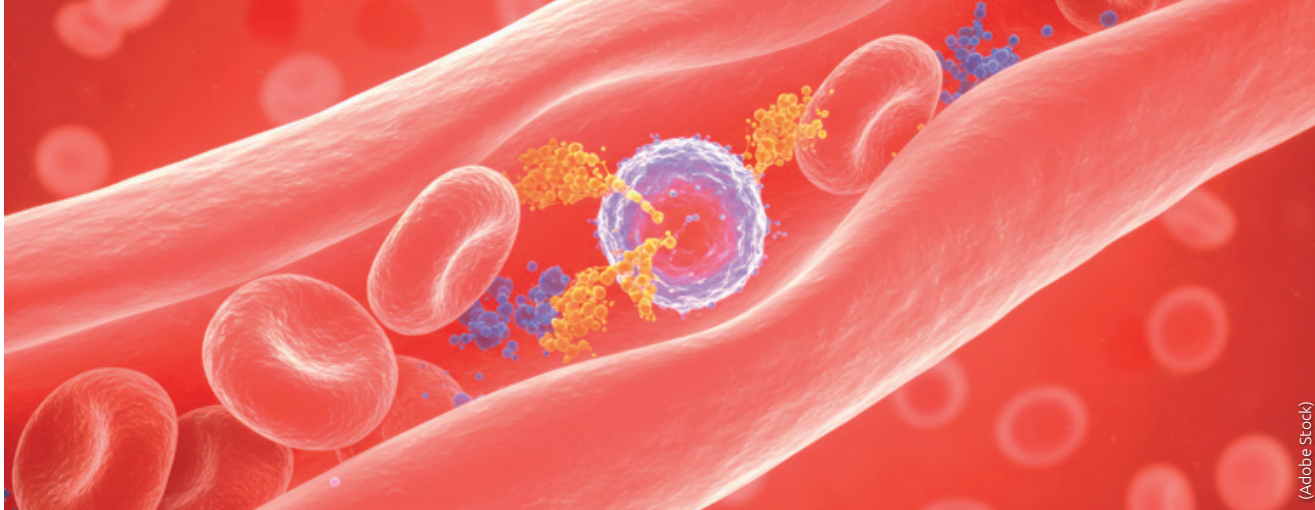
Calprotectin is released directly at sites of inflammation and therefore more closely reflects local immune activation than conventional non-specific markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which are largely hepatocyte-driven [2,4].

It is a potent acute-phase reactant, with circulating levels increasing more than 100-fold during active inflammation and dropping with effective treatment [1,3,4]. Importantly, unlike CRP, cCALP is not suppressed by interleukin-6 (IL-6) blocking agents, making it a useful alternative marker in patients receiving these biologic therapies [2,3].

Furthermore, calprotectin is stable at room temperature and is easily measurable in serum, facilitating its wider use in clinical practice [1,2].

Elevated levels in SARDs

Elevated cCALP levels have been reported in a range of SARDs. The most extensively studied of these is rheumatoid arthritis (RA), which is the most common chronic inflammatory joint disease. High concentrations of calprotectin are found in the synovial fluid of active arthritis joints of RA patients. Owing to its low molecular weight, calprotectin can diffuse into the circulation, and there is



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a good correlation between serum cCALP and synovial levels [2]. Clinically, cCALP levels are significantly higher in patients with active disease compared with those in remission or healthy controls [1–4].

Similarly, elevated cCALP levels have been demonstrated in patients with other SARDs compared to healthy controls, for example in psoriatic arthritis (PsA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), Sjögren’s disease (SjD) and microscopic polyangiitis (MPA) [1–3].

Association with autoantibodies

Serologically, a relationship between cCALP and autoantibody markers has been demonstrated in multiple SARDs. In RA, cCALP levels correlate with rheumatoid factor and anti-cyclic citrullinated peptide antibodies, with higher cCALP levels observed in seropositive than in seronegative patients [2,4].

cCALP is also associated with high levels of anti-dsDNA antibodies in SLE, and with the presence of anti-Scl70, anti-histone and anti-U1RNP antibodies in SSc [1,3]. In SjD, correlations have been described with anti-SSA, anti-Ro60 and anti-SSB antibodies [2,3].

Correlation with disease activity

In many SARDs, cCALP shows a positive correlation with established measures of disease activity. In RA, cCALP correlates with the Disease Activity Score for 28 joints (DAS28), ultrasound-detected synovitis and CRP levels [1,2,4,5]. cCALP is also independently associated with radiographic progression, with high baseline levels predictive of future erosive damage [1,2].

Correlations between cCALP and disease activity indices have also been demonstrated in SLE, PsA, SjD, and ANCA-associated vasculitis [1, 2]. Notably, in several SARDs, cCALP has been described as a more sensitive marker of disease activity than conventional markers such as CRP and ESR [1,2,4,5].

cCALP may also be associated with specific or severe manifestations. In SSc, high cCALP levels are associated with lung fibrosis [1,2] and are predictive of reduced survival [1,3]. Further associations include carotid atherosclerosis in SjD [2,3], as well as glomerulonephritis, cerebrovascular events and acute myocardial infarction in SLE [1,2]. These findings suggest that cCALP may aid the identification of patients who need tight follow-up or who might benefit from preventive treatment.

Predictive value for therapeutic response

cCALP is a sensitive and specific indicator of therapy response across different SARDs, including RA, SLE, PsA and ANCA-associated vasculitis [2]. Baseline cCALP levels predicted responses to both conventional agents such as methotrexate and biologic disease-modifying anti-rheumatic drugs (DMARDs) in RA patients [2,4]. Furthermore, individuals who responded to biologic therapies exhibited higher baseline cCALP levels than non-responders, suggesting a potential role as a predictive marker of therapy response [2,4].

Standardized cCALP measurement

Calprotectin levels can be measured using immunoassay-methods, such as enzyme-linked immunosorbent assay (ELISA) and chem-illuminescence immunoassay (ChLIA). These assays

enable, standardized sensitive and quantitative measurements and offer a high degree of automation. >>

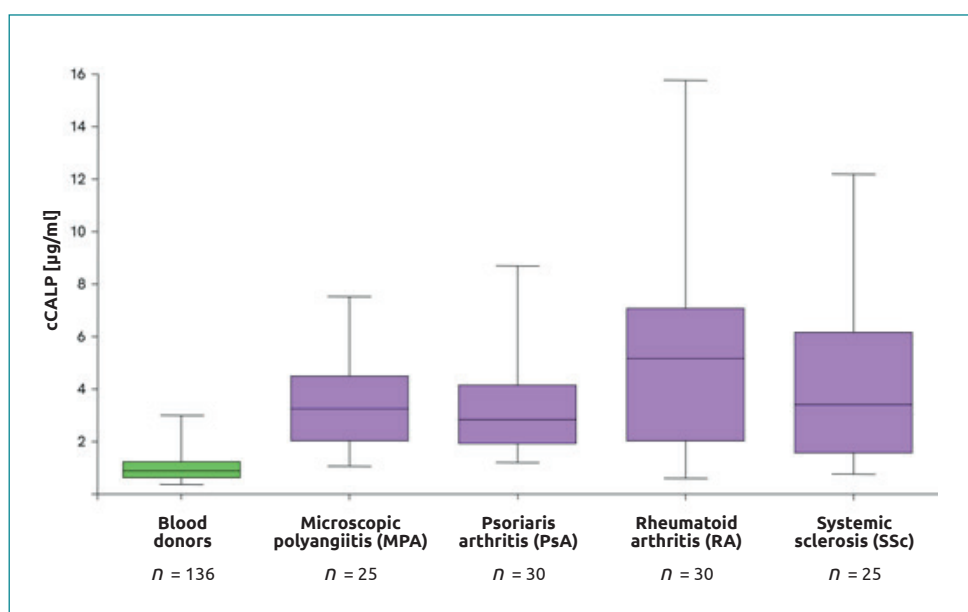


Figure 1. cCALP levels in different cohorts measured using the Euroimmun Circulating Calprotectin ELISA

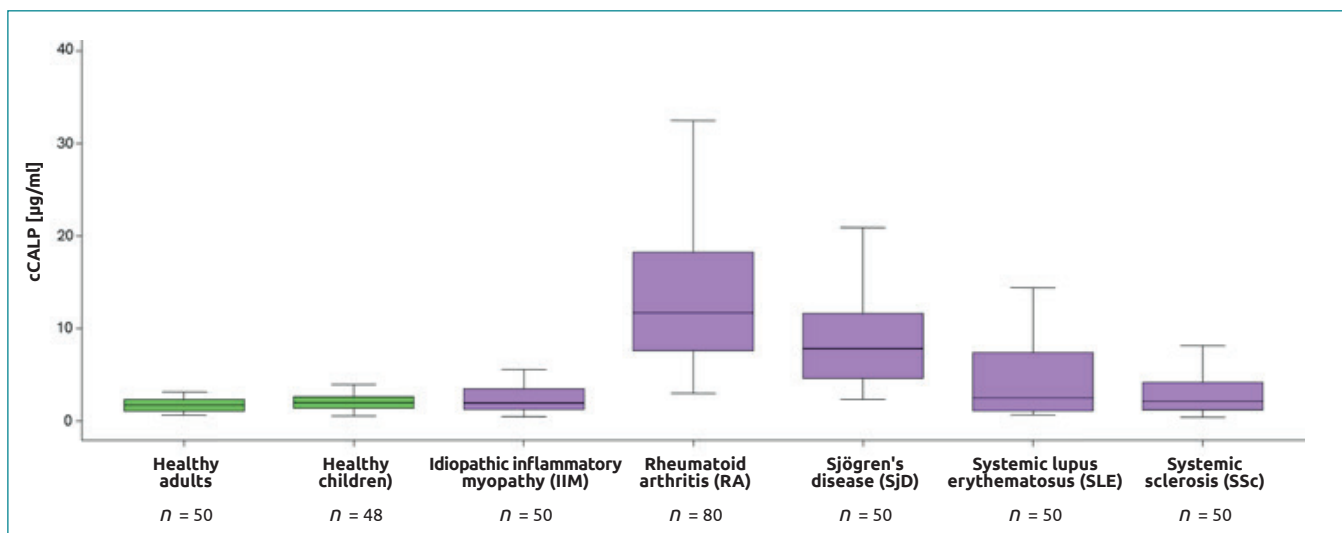


Figure 2. cCALP levels in different cohorts measured using the IDS Fluid Calprotectin ChLIA

ELISA and ChLIA tests for measurement of cCALP in serum have been developed by Euroimmun and Immunodiagnostic Systems (IDS), complementing existing assays for determination of fCALP in stool samples. The assays are based on antibodies that are highly specific for the biologically active calprotectin heterocomplex, avoiding cross reactions with the calprotectin subunits calgranulin A (S100A8) and calgranulin B (S100A9) and the structurally similar antigen A100A12.

Clinical performance

In clinical performance studies, cCALP was measured in serum samples from patients diagnosed with RA ($n = 30$), SSc ($n = 25$), PsA ($n = 30$) or MPA ($n = 25$) and from blood donors ($n = 136$) using the Euroimmun Circulating Calprotectin ELISA (Fig. 1). A general trend towards increased cCALP levels was seen in all patient groups compared with the healthy control groups. The analysis demonstrated statistically significantly higher cCALP levels in patients with inflammatory rheumatic diseases compared to healthy controls ($P < 0.0001$).

In a collaborative study between Euroimmun and the University of Liège (Belgium), cCALP was measured in a cohort of serum samples from patients with RA ($n = 80$), SLE ($n = 50$), SjD ($n = 50$), SSc ($n = 50$) or idiopathic inflammatory myopathy ($n = 50$) and from healthy adults ($n = 50$) and children ($n = 48$) using the Euroimmun Circulating Calprotectin ELISA and the IDS Fluid Calprotectin ChLIA (Fig. 2). Both tests revealed higher concentrations of cCALP in patients with auto-

immune diseases compared with healthy controls. Regression analysis revealed a high level of agreement between the ELISA and the ChLIA [6,7].

Summary

cCALP is a sensitive biomarker of inflammation that correlates with disease activity and the presence of autoantibodies in different SARDs. Elevated levels are typically associated with worse structural outcomes and may predict disease relapse or severe manifestations. Compared with conventional markers such as CRP, cCALP may provide additional sensitivity, particularly in patients who do not show changes in traditional inflammatory markers or who are receiving IL-6 targeted therapies. Furthermore, cCALP shows promise as a biomarker for monitoring therapeutic response, supporting clinical decision-making – particularly when considering treatment tapering. Future studies will explore the pathogenic role of calprotectin and further define its clinical utility as a biomarker in SARDs and other inflammatory diseases.

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References

- Ometto F, Friso L, Astorri D et al. Calprotectin in rheumatic diseases. *Exp Biol Med* (Maywood). 2017;242(8):859–873 (<https://doi.org/10.1177/1535370216681551>).
- Manfredi M, Van Hoovels L, Benucci M et al. Circulating calprotectin (cCLP) in autoimmune diseases. *Autoimmun Rev*. 2023;22(5):103295 (<https://doi.org/10.1016/j.autrev.2023.103295>).
- Carnazzo V, Redi S, Basile V et al. Calprotectin: two sides of the same coin. *Rheumatology* (Oxford). 2024;63(1):26–33 (<https://doi.org/10.1093/rheumatology/kead405>).
- Abildtrup M, Kingsley GH, Scott DL. Calprotectin as a biomarker for rheumatoid arthritis: a systematic review. *J Rheumatol*. 2015;42(5):760–770 (<https://doi.org/10.3899/jrheum.140628>).
- Hurnakova J, Hulejova H, Zavada J et al. Relationship between serum calprotectin (S100A8/9) and clinical, laboratory and ultrasound parameters of disease activity in rheumatoid arthritis: a large cohort study. *PLoS One*. 2017;12(8):e0183420 (<https://doi.org/10.1371/journal.pone.0183420>).
- Hoffmann K, Herbst V, Silvestric-Scheel et al. Newly developed ELISA for detection of circulating calprotectin in serum and plasma. Oral presentation at the 15th International Congress on Autoimmunity 2026; Abstracts E-Book SO144/#132. Prague, Czech Republic (https://info.kenes.com/Flip/AUTO26_Abstract_Book/).
- Silvestric-Scheel, Pham H, Hoffmann K et al. Newly developed ChLIA for detection of fluid calprotectin in serum. Poster presentation at the 15th International Congress on Autoimmunity 2026; Abstracts E-Book EP094/#131. Prague, Czech Republic (https://info.kenes.com/Flip/AUTO26_Abstract_Book/).