Review paper

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Calprotectin in rheumatic diseases: a review

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Abstract

Calprotectin also known as MRP8/14 or S100A8/A9 is a heterodimeric complex of two S100 calcium-binding proteins: myeloid-related protein 8 (MRP-8 or S100A8) and MRP-14 (or S100A9). At present, according to many authors, it is considered that calprotectin MRP8/14 is a potentially more sensitive biomarker of disease activity in rheumatoid disease than conventional inflammatory indices such as the erythrocyte sedimentation rate, C-reactive protein and others. A review of the literature on concentration of calprotectin in patients with some rheumatic diseases (rheumatoid arthritis, juvenile idiopathic arthritis, adult-onset Still's disease, systemic vasculitis, polymyalgia rheumatica, ankylosis spondylitis, systemic lupus erythematosus, and primary Sjögren's syndrome) is presented.

Key words: calprotectin, inflammation, inflammatory markers.

Calprotectin, also known as MRP8/14 or S100A8/A9, is a heterodimeric complex of two S100 calcium-binding proteins: myeloid-related protein 8 (MRP-8 or S100A8) and MRP-14 (or S100A9). Calprotectin is an important proinflammatory factor of innate immunity acting as endogenous damage-associated molecular pattern molecule via toll-like receptor 4 activation [1]. Calprotectin was isolated for the first time from granulocytes by Fagerhol et al. [2] in 1980 and named L1 protein. The term calprotectin was proposed later, reflecting its protective role in epithelial defense, and its fungicidal and bactericidal activity. MRP8/14 can be detected in the plasma of all healthy subjects. The normal level is in the range 1–6 mg/l, and it increases in response to various tissue injuries and inflammation [3]. Calprotectin released from activated granulocytes and macrophages during inflammation, expresses a proinflammatory effect *in vitro* on the phagocytes and endothelial cells and promotes inflammation *in vivo* [4]. A high calprotectin concentration was found in synovial fluid obtained from the joints of rheumatoid arthritis patients, while a low concentration was found in those with osteoarthritis [5]. MRP8/14 has a molecular weight of only 36.5 kDa and thus may diffuse from inflamed joints into the circulation, where it can be measured in plasma; however, the half-life of calprotectin in plasma is only 5 hours [6].

At present, according to many authors it is considered that calprotectin MRP8/14 is a potentially more sensitive biomarker of the disease activity in rheumatoid disorders than conventional inflammatory indices such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), because it directly reflects inflammation in the synovium [7]. Numerous studies have shown that alterations of calprotectin level are associated with disease activity in patients with rheumatoid arthritis (RA) [8], Still's disease [9], ankylosis spondylitis (AS) [10], psoriatic arthritis (PsA) [11], primary Sjögren's syndrome (pSS) [12], juvenile idiopathic arthritis (JIA) [13] and systemic lupus erythematosus (SLE) [14]. Concentration of calprotectin was also elevated in patients with Crohn's disease and ulcerative colitis [15], which is often used in diagnostics and monitoring of these illnesses.

Rheumatoid arthritis is a chronic inflammatory disease leading to joint destruction. Since calprotectin is released from activated granulocytes and monocytes/macrophages in inflamed joints, plasma concentration of this protein may reflect the amount or expansion of local inflammation and thus is rather directly related to the joint damage in rheumatoid arthritis [16]. The results

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of the study by Choi et al. [8] show that in RA patients serum levels of MRP8/14 were related to clinical signs and symptoms, and MRP8/14 at baseline might be used to predict the future response to targeted treatment independently of the specific mechanism of drug action. They suggested that serial measurement of MRP8/14 level in serum could be used to monitor the early response to treatment, and to predict the clinical response [8]. Treatment with adalimumab, infliximab or rituximab lowered the level of MRP8/14 significantly in the combined group of good and moderate responders, but not in non-responders. This change already reached statistical significance after 4 weeks for the groups receiving adalimumab or infliximab, suggesting that MRP8/14 could be used to monitor the early response to tumour necrosis factor α inhibitors (anti-TNF-α) treatment and to predict subsequent clinical response. In the rituximab group, a decrease in MRP8/14 serum level was found after 4 weeks in responders but the finding was not statistically significant. Sixteen weeks after initiation of the treatment a significant decrease in MRP8/14 serum level was observed in the responders, but not in non-responders.

Inciarte-Mundo et al. [17] in a cross-sectional study included 87 patients with rheumatoid arthritis, receiving adalimumab, etanercept or infliximab for at last 3 months. They demonstrated that calprotectin stratified disease activity in rheumatoid arthritis patients receiving TNF-α inhibitors more accurately than the acute-phase reactants such as CRP and erythrocyte sedimentation rate (ESR), whichever composite index was assessed (the Disease Activity Score in 28 joints [DAS28], the Clinical Diseases Activity Index [CDAI] or the Simplified Disease Activity Index [SDAI]). Only calprotectin level distinguished between RA patients in clinical remission and those with low disease activity according to all indices analyzed. MRP8/14 serum level correlated inversely with TNF-α inhibitors trough serum levels [17]. In another study, Inciarte-Mundo et al. [18] analyzed associations between calprotectin, ESR, CRP and disease activity indices in 33 RA patients receiving tocilizumab. Serum calprotectin level was higher in patients than in healthy controls. Calprotectin levels did not differ according to age or sex. Calprotectin level, but not CRP or ESR strongly correlated with all composite disease activity indices [18].

Serum MRP8/14 level was shown to correlate with disease activity levels and is independently associated with radiographic progression in RA [16]. All patients were examined with hand radiographs, and radiographic damage was scored according to van der Heijde's modification of Sharp's method.

Incierte-Mundo et al. [11] in a study of 92 patients (42 with rheumatoid arthritis and 50 with psoriatic arthritis) receiving adalimumab, etanercept or infliximab analyzed the relations of calprotectin and synovitis detected with power Doppler ultrasound (PDUS). Power Doppler detects synovial flow, a sign of increased synovial vascularization and a better estimate of active synovial inflammation compared with measurement of synovial hypertrophy [19]. PDUS correlates with diseases activity and decreases after treatment, and it is therefore sensitive to change [20]. Synovial hypertrophy and power Doppler signals were graded using a four-grade semi-quantitative scoring system according to the methodology of Szkudlarek et al. [21].

Patients with PDUS detectable synovitis had a higher calprotectin level and lower TNF-inhibitor trough serum levels, reflecting local, ongoing synovial inflammation [11]. Calprotectin was more accurate than ESR or CRP in detecting PDUS synovitis in the rheumatoid arthritis and psoriatic arthritis patients. Tumor necrosis factor α inhibitor trough serum levels inversely correlated with the PDUS score and calprotectin level [11]. Calprotectin may help clinicians identify US detectable active synovitis in rheumatoid and psoriatic arthritis patients in clinical remission or with low disease activity treated with TNF-α inhibitors [11].

Moncrieffe et al. [22] in a subgroup of juvenile idiopathic arthritis patients, tried to define the prognostic value of baseline serum MRP8/14 protein and clinical variables in response to methotrexate (MTX) therapy. In this study, the authors demonstrated the potential of MRP8/14 to identify a subset of patients who respond well to MTX. This pattern of high disease activity prior to treatment correlating with good response was also observed for other parameters: CRP, join count and physician's global assessment as well as for proinflammatory cytokines (IL-1β, IL-6, IL-18, IL-22) [22]. MRP8/14 has higher specificity for distinguishing patients who will be good responders than any other single variable [22], and this finding may be applicable for clinical practice. In this study, a high level of MRP8/14 correlated with a high risk of relapse after discontinuation MTX administration.

Guo et al. [23] reported that calprotectin concentrations were significantly higher in patients with adult-onset Still disease (AOSD) compared to patients with rheumatoid arthritis, primary Sjögren's syndrome, systemic lupus erythematosus and healthy controls. Serum MRP8/14 was positively correlated with ferritin and concentration of hemoglobin was significantly lower in patients with a high calprotectin level compared to those with low level of the protein [23]. These findings suggest that serum calprotectin may serve as a promising marker for the diagnosis of adult-onset Still's disease and for monitoring of the disease activity [23].

The observation of Oktayoglu et al. is surprising [10]. The aim of their study was to investigate the serum level of calprotectin in patients with AS and its association with disease activity. Thirty-one patients who met the modified New York criteria for AS and 45 healthy controls were included in this study. Mean serum level of calprotectin was significantly higher in the patients with AS compared with healthy controls (p = 0.003). However, the calprotectin levels did not correlate with the measurements of disease activity, functional abilities, radiological damage, or the quality of life in these patients [10].

Elevated serum levels of calprotectin were also observed in patients with Behçet's disease, a form of systemic vasculitis. Serum level of calprotectin in patients with Behçet's diseases did not correlate with CRP levels, ESR, WBC (white blood cell) count or BDCAF score (Behçet's disease current activity form) [24]. Hirono et al. [25] observed elevated serum levels of MRP8/14 in patients with Kawasaki disease and concluded that the circulating level of this complex protein might be a predictor of the severity of vasculitis.

Brun et al. [26] found that in patients with polymyalgia rheumatica or temporal arteritis serum calprotectin level correlated significantly with other acute phase parameters: ESR, CRP, fibrinogen, orosomucoid, haptoglobin. Calprotectin was significantly decreased after introduction of treatment with prednisolone orally and correlated with the daily dosage of this glucocorticosteroid.

Relatively limited data were found about the calprotectin concentration in SLE patients. In 2016, Tantivitayakul et al. [27] reported that myeloid-related proteins MRP8 and MRP14, also known as the DAMPs (damage associated molecular pattern molecules) significantly correlated with the early loss of the kidney function (correlation with severe forms of glomerulonephritis) in SLE patients and with their therapeutic response. Moreover, according to Tydén et al. [28] elevated serum levels of S100A8/A9 in SLE patients may be used as an indicator of severe cardiovascular disease, suggesting that SLE patients with elevated serum S100A8/A9 concentrations may benefit from more intense cardiovascular primary preventive strategies and possibly also from more intense and early immunosuppressive treatment.

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In summary, it can be concluded that calprotectin can play a crucial role as a significant marker of inflammation in many different rheumatoid diseases. Further investigations are needed to elucidate the calprotectin – inflammation relationship and its application for clinical practice.

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