REVIEW

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S100A8/A9 as a biomarker for synovial inflammation and joint damage in patients with rheumatoid arthritis

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S100A8 and S100A9 are major leukocyte proteins, known as damage-associated molecular patterns, found at high concentrations in the synovial fluid of patients with rheumatoid arthritis (RA). A heterodimeric complex of S100A8/A9 is secreted by activated leukocytes and binds to Toll-like receptor 4, which mediates downstream signaling and promotes inflammation and autoimmunity. Serum and synovial fluid levels of S100A8/A9 are markedly higher in patients with RA than in patients with osteoarthritis or miscellaneous inflammatory arthritis. Serum levels of S100A8/A9 are significantly correlated with clinical and laboratory markers of inflammation, such as C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, and the Disease Activity Score for 28 joints. Significant correlations have also been found between S100A8/A9 and radiographic and clinical assessments of joint damage, such as hand radiographs and the Rheumatoid Arthritis Articular Damage score. In addition, among known inflammatory markers, S100A8/A9 has the strongest correlation with total sum scores of ultrasonography assessment. Furthermore, baseline levels of S100A8/A9 are independently associated with progression of joint destruction in longitudinal studies and are responsive to change during conventional and biologic treatments. These findings suggest S100A8/A9 to be a valuable diagnostic and prognostic biomarker for RA.

Keywords: S100A8; S100A9; Arthritis, rheumatoid; Biological markers

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by synovial inflammation, destruction of joint cartilage and bone erosion. Although the etiopathology of RA remains unclear, the infiltration of inflammatory leukocytes, primarily macrophages, proliferation of synovial fibroblasts and local production of proinflammatory cytokines play significant roles in disease progression [1,2]. The acti-

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vation of synovial macrophages or synovial fibroblasts may trigger the activation of lymphocytes and subsequent inflammation in synovium since inactivating these cells reduces arthritis in experimental models [3]. Early diagnosis is of particular interest in this potentially aggressive disease to prevent joint deformity and functional impairment.

The management of RA depends on an exact measurement of disease activity, as well as early diagnosis [4,5]. A biomarker reflecting the amount of inflammation and joint destruction would aid in RA prognosis and be clinically helpful in optimizing individualized medical treatment. Early stages of RA development can be predicted using clinical and serological measures [3,6,7]. Inflammatory markers can also facilitate detection of residual disease activity and be used to adjust individual treatment needs. Thus far, the erythrocyte sedimentation rate (ESR) and the acute phase protein C-reactive protein (CRP) are the most widely used laboratory markers for evaluation of inflammatory activity in patients with RA [8-10]. Recently, the multibiomarker disease activity (MBDA) test, measuring various biomarkers, has proven useful for objectively assessing disease activity in patients with RA. However, the currently available biological tests are not predictive for radiographic progression [11].

THE S100 PROTEINS

The S100 proteins are major monocyte/macrophage proteins that bind calcium, constituting ~40% of the cytosolic protein in neutrophil granulocytes [12-15]. Currently, more than 20 members of the S100 family have been identified [16,17]. These proteins belong to the damage-associated molecular patterns family, also called alarmins, and are the endogenous molecules that signal the early phase of tissue and cell damage [18-20]. The major source for extracellular S100 proteins is via active nonclassical secretion rather than passive release from necrotic cells [21]. The S100 proteins have a critical role in inflammation as they can activate the innate immunity pathway mediated by Toll-like receptors (TLR) or receptors for advanced glycation end products (RAGE) [22,23]. The TLR- or RAGE-mediated signal transduction pathways result in up-regulation of a wide range of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1b, and IL-6 [24,25].

The most familiar S100 protein is S100A8/A9, also known as myeloid-related protein (MRP)-8/MRP-14, calprotectin, the L1 protein [14] or calgranulin A and B [26]. The human S100A8 protein is comprised of 93 amino acids and has a molecular weight of 10.8 kDa. The human S100A9 protein consists of 114 amino acids with a molecular weight of 13.2 kDa [26]. Expression of these S100 proteins in monocytes and macrophages is restricted to early differentiation stages and declines rapidly during maturation. The preferred form for human S100A8 and S100A9 is the S100A8/S100A9 heterodimer [17]. The S100A8/A9 protein is released during the activation and turnover of leukocytes [27] and highly up-regulated in various autoimmune disorders [28]. In RA, levels of S100A8/A9 are increased locally at sites of inflammation, such as in the synovial fluid (SF) [26,29] and synovial tissue, as well as in the circulation [30]. Moreover, S100A8/A9 levels are strongly associated with disease activity in patients with RA [31].

THE S100A8/A9 PROTEIN: THE MOST ABUNDANT PROTEIN IN RA SYNOVIAL FLUID

The synovium-cartilage junction is a critical zone in the development of RA [32], suggesting that disease-specific proteins may be localized in SF rather than in other biological materials. High S100A8/A9 concentrations have been found in the SF from RA patients, while low concentrations were found in osteoarthritic patients [33]. Proteomic analysis of SF in patients suffering from RA, osteoarthritis (OA), and miscellaneous inflammatory arthritis (MIA) confirmed that S100A8, S100A9 and S100A12, another S100 protein, are the most differentially expressed biomarkers and are overexpressed in RA SF, but not in SF from OA or MIA patients [33]. Although synovial levels of these proteins discriminate RA from OA or MIAs with high sensitivity and specificity, no significant correlation was demonstrated between synovial polymorphonuclear cell concentration and S100A8 and S100A9 levels [33]. This suggests that these biomarkers are produced by neutrophil effusion and by the RA synovial membrane. Moreover,

an increase in S100A8 and S100A9 mRNA expression by fibroblast-like synoviocytes (FLS) in a murine model of RA has been reported and both S100A8 and S100A9 proteins were detected in synovial resident cells in the cartilage-pannus junction of RA synovial membranes [34]. In a recent report in Korean patients, S100A8/9 levels in RA SF were significantly increased in comparison with OA SF. Additionally S100A8 induced Th17 cell differentiation through upregulation of IL-6 expression by RA FLS via TLR4/phosphoinositide 3-kinase/nuclear factor-kB, and mitogen-activated protein kinase signaling pathways [35].

THE S100A8/A9 PROTEIN: CORRELATION WITH LABORATORY AND CLINICAL ASSESSMENTS

S100A8/A9 has a molecular weight of only 36.5 kDa [36], and may diffuse from inflamed joints into the blood circulation, where it can be measured in serum. Previously, a significant correlation was found between S100A8/A9 levels in serum and SF [26,37]. The serum concentration of this protein may reflect the amount of local inflammation and thus be related to joint damage in RA. In a cross sectional analysis of 145 RA patients, the serum concentration of S100A8/A9 correlated significantly ($p < 0.001$) with both laboratory tests for CRP and ESR, as well as clinical examinations including Disease Activity Score for 28 joints (DAS28), 28-swollen joint counts (SJC), and physical global visual analogue scale (Table 1) [37]. Considerably higher S100A8/A9 levels ($p < 0.001$) were found in rheumatoid factor (RF) positive patients compared with RF negative patients [37].

In a 10-year follow-up study of patients with RA, strong correlations were found at baseline/follow-up between S100A8/A9 and CRP or ESR [38]. In addition, patients positive for anticyclic citrullinated protein antibodies (anti-CCP), IgA RF, or IgM RF had higher S100A8/A9 levels at baseline and at follow-up than patients who are negative for these serological markers ($p < 0.001$). Of the inflammatory variables, the magnitude of the regression coefficient for S100A8/A9 was only marginally influenced by addition of CRP, ESR, and anti-CCP, whereas the regression coefficients for CRP and ESR were markedly decreased when S100A8/A9 was added to the linear regression equation [34].

In patients with recent onset disease modifying antirheumatic drug/glucocorticoid (GC)-naïve RA, serum levels of S100A8/9 were significantly elevated compared to those of healthy controls at baseline but were normalized with a significant reduction in disease activity after 3 months of conventional treatment [38]. The levels of S100A8/9 were not affected by different doses of GCs and/or methotrexate. Changes in serum levels of S100A8/9 positively correlated with changes in serum levels of CRP ($r = 0.476$, $p = 0.002$), changes in DAS28 ($r = 0.390$, $p = 0.01$), and changes in SJC ($r = 0.539$, $p < 0.001$). Furthermore, decreases in S100A8/9 rather than CRP levels were associated with improvements in the total number of swollen joints over time ($p = 0.001$) [38]. This result suggests that decreases in serum S100A8/9 over time can predict improvements in the number of RA affected joints.

In an investigation examining the associations between levels of the inflammatory biomarkers and B-mode/power Doppler (BM/PD) scores from a comprehensive ultrasonography (US) examination over a 12-month period of treatment with adalimumab, significant correlations were found between the levels of S100A8/9 and the US scores [39]. S100A8/9 showed the highest correlation coefficients compared with serum amyloid A (SAA), CRP and ESR and the validity of S100A8/9 as an inflammatory marker was further supported by associations with the clinical evaluation of

Table 1. Spearman's rank correlations between serum levels of S100A8/A9 and other laboratory and clinical assessments

	CRP	ESR	DAS28	SJC	Reference
S100A8/A9	0.57	0.50	0.55	0.49	[37]
	0.59	0.67	NA	NA	[43]
	0.439	NA	0.501	0.443	[38]

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS28, Disease Activity Score for 28 joints; SJC, swollen joint counts; NA, not assessed.

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disease activity. S100A8/9 was also shown to have a higher response to change from biologic treatment than CRP, SAA, or ESR. Regression analyses showed S100A8/A9 was independently associated with both total sum BM and PD scores, even when DAS28 was included in the equation [39]. This finding of associations between S100A8/A9 and the US sum scores suggests that in RA patients a normal S100A8/A9 level may be considered as a marker of clinical remission. Thus, multiple determinations of inflammatory markers, including serum levels of S100A8/A9, can further improve the diagnostic utility of detecting subclinical disease activity in RA patients.

THE S100A8/A9 PROTEIN: CORRELATION WITH RADIOGRAPHIC ASSESSMENT

Radiographic damage is considered a key end-point in clinical studies of RA and is associated with long-term physical disability [40]. Previous studies have shown that acute-phase reactants, RF, and anti-CCP predicted subsequent progression of radiographic damage [40-42], but it has not been possible to develop a clinically useful algorithm for prediction of radiographic progression in early RA.

S100A8/9 has been consistently associated with two measures of joint damage; van der Heijde modified Sharp score and the Rheumatoid Arthritis Articular Damage (RAAD) score [37,43]. After correcting for CRP, ESR, RF, DAS28, gender, and age in a multiple regression analysis, S100A8/9 remained significantly associated with the modified Sharp score (p = 0.018) and RAAD score (p = 0.04). The S100A8/A9 quartiles, which were divided based on the S100A8/A9 concentrations, revealed significant differences (p < 0.001) when they are analyzed based on the modified Sharp and RAAD scores. Of the inflammatory variables, only S100A8/9 was independently associated with joint damage.

The correlation between serum S100A8/A9 and disease progression in the modified Sharp and the RAAD scores was maintained during a 10-year longitudinal study [43]. When the patients were divided into three groups based on baseline levels of S100A8/A9, the SharpProgScore and RAAD score are significantly different between the groups (p < 0.001). Among the inflammatory variables, only baseline S100A8/9 level remained significantly associated with the SharpProgScore (p = 0.045) and RAAD score (p = 0.012) in multiple linear regression analyses with adjustments for baseline levels of CRP, ESR, and anti-CCP, as well as gender, age, and disease duration. Neither CRP nor ESR had significant associations with the two outcome variables for joint damage in corresponding analyses. Importantly, S100A8/9 remained an independent predictor of joint damage in multivariate analyses adjusted for anti-CCP levels [37].

S100A8/A9 AS A COMPONENT OF THE MBDA TEST FOR RHEUMATOID ARTHRITIS

Several studies in RA patients have shown improved outcomes with tight control of disease activity, a strategy employing frequent disease activity measurement and treatment adjustment to reach a specific target disease activity level [44-46]. Treat to target guidelines codified these results into specific recommendations for optimal care including frequent disease activity monitoring for all patients [47].

Current recommendations for treatment of RA advise measuring disease activity as frequently as monthly for patients with moderate to high disease activity, and less frequently every 3 to 6 months for patients with sustained low disease activity or remission [47]. Measurements of disease activity in the clinic may include symptom assessment, joint counts, CRP, ESR, or some combination of these, indexed as a disease activity score based on DAS28, Clinical Disease Activity Index, Simplified Disease Activity Index, or Routine Assessment of Patient Index Data [48,49]. These clinical assessments depend upon patient and/or physician judgments and are subject to intra-assessor and interassessor variability [50,51], whereas laboratory tests—such as ESR and CRP—are general measures of inflammation that can be normal in ~40% of RA patients [52].

Recent advances in biomarker analysis have enabled the development of MBDA tests, which are impacting patient care and outcomes in various therapeutic areas. Tests based on serum protein levels have been introduced for RA and application in RA. An MBDA test measuring serum levels of 12 proteins has proven useful in assessment of RA disease activity [11,53].

The MBDA score was calculated using the concentration of 12 biomarkers (SAA, IL-6, TNF-RI, vascular endothelial growth factor A, matrix metalloproteinase 1 [MMP-1], cartilage glycoprotein 39 [YKL-40], MMP-3, epidermal growth factor, vascular cell adhesion molecule 1, leptin, resistin and CRP). MBDA scores were consistently associated with clinical activity levels, such as SJC, tender joint counts, DAS28-CRP [11,53]. This score using biomarker levels may enable objective measurements of the disease processes underlying RA. However, this MBDA test was not predictive for radiographic progression [11].

Although S100A8/A9 was not included in the present MBDA scores, it has potential as a biomarker. As mentioned above, S100A8/A9 was strongly correlated with clinical disease activity, as well as radiographic assessment. Serum levels of S100A8/A9 have been shown to be a reliable biomarker of diagnosis and prognosis for RA [37]. Further prospective studies are needed to identify the optimal use of a new MBDA score including S100A8/A9 in the management of RA.

CONCLUSIONS

S100A8/A9 is the most enriched protein in RA SF and was correlated significantly and independently with laboratory and clinical assessments of synovial inflammation, as well as radiographic and clinical assessments of joint damage. The validity of S100A8/9 as a biomarker is different from other acute phase proteins since S100A8/9 is released from activated leucocytes in the inflamed synovium, thus directly reflecting the leukocyte levels in inflamed joints of RA patients. In clinical practice, some patients have normal or low levels of CRP and ESR despite extensive arthritis. Therefore, S100A8/9 could be a useful inflammatory marker in these patients.

In a recent long-term follow-up study [43], baseline S100A8/9 levels remained an independent predictor of clinical and radiographic joint damage after 10 years, indicating that S100A8/A9 may be a suitable prognostic biomarker for erosive disease in patients with RA. S100A8/A9 was also associated with the sum scores from a comprehensive US assessment and was responsive to change during anti-TNF treatment [39]. Thus, examination of this leukocyte protein could be of additional value in the assessment of RA patients on biologic treatment. A recent study of patients with juvenile idiopathic arthritis in remission shows that the level of S100A8/A9 was associated with risk of relapse after discontinuing methotrexate [54], adding more value to S100A8/A9 as a predictive biomarker. Furthermore, S100A8/A9 was a sensitive biomarker in cryopyrin-associated periodic syndromes, identifying patients who need to adjust their therapy or should be switched to other drugs [55].

Validation criteria for biomarkers need to be developed in a larger cohort of patients to address structural damage outcomes, assay reproducibility, and reliability. In addition, further longitudinal studies employing a large population of RA patients without destructive disease are required to address whether S100A8/9 levels improve the prediction of long-term joint damage in a highly sensitive and reliable manner in patients with RA. Determination of S100A8/A9 level, in addition to levels of existing inflammatory markers, can assist in the detection of subclinical and residual disease activity and could be valuable in adjusting individual treatment in RA patients.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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