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## Acute Phase Proteins in Prototype Rheumatic Inflammatory Diseases

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### 1. Introduction

The term “acute phase” was first coined by the group of Avery (Abernethy and Avery 1941; Macleod and Avery 1941) in reference to serum of an acutely ill patient with an infectious disease. At first, C-reactive protein (CRP) was described as one of the major components of this phase (as reviewed in Pepys and Baltz, 1983 (Pepys and Baltz 1983), however since then a more detailed description of the acute phase has emerged. Today, it is regarded to include a broad scope of processes and mechanisms comprising of neuroendocrine, hematopoietic, metabolic and hepatic changes, as well as modulations in nonprotein plasma constituents (Gabay and Kushner 1999).

The acute phase response (APR) is caused by the triggering of environmental factors, such as bacteria, viruses, injury and wound repair, autoimmunity, neoplasia in combination with stress, systemic and cellular senescence. The organism reacts to disrupted homeostasis with an influx of local cells involved in inflammation (such as polymorphonuclear leukocytes, monocytes, macrophages, lymphocytes) secreting a number of cytokines (most notably interleukins IL-1, IL-6 and tumour necrosis factor - $\alpha$  (TNF- $\alpha$ )) and chemokines (such as IL-8) into the bloodstream. This stimulates production of acute phase proteins (APPs) by the liver and their secretion into the blood circulation, all of which constitute the APR. Resolution of this response brings about, among other processes, wound healing, bacterial and viral clearance, removal of antigen-autoantibody complexes, breakdown and removal of cellular debris, and ultimately leads to the return of APPs to basal levels. APPs can be divided (based on their levels of production and detection in the circulation) into 4 groups (Table I).

#### 1.1 Major APPs

Proteins with a > 5-fold change in their serum levels during APR are considered as major APPs (Table I). In humans the two **major** APPs are CRP and serum amyloid A (SAA), the levels of which start elevating approximately 4 hours after the initial stimulus (e.g.infection), and can reach up to 1000x greater than physiological levels following 24-72hs (Gabay and Kushner 1999). CRP is the standard inflammatory biomarker measured in humans routinely. SAA levels correlate to CRP in the majority of diseases, however, when CRP is low (even when inflammation is present) SAA can be used as an excellent alternative clinical marker (Malle and De Beer 1996). In addition to being markers of disease detection, both

CRP and SAA are also thought to actively participate in disease progression (with cytokine-like and chemoattractant properties, stimulation of matrix metalloproteinases, among other processes), and/or during the resolution phases of the APR (such as serving as opsonins). SAA is an evolutionarily conserved protein involved in innate immunity (Uhlir and Whitehead 1999). In addition to being a major APP, SAA has been reported to be a marker of rheumatoid arthritis (RA) (Cunnane, Grehan et al. 2000) and a predictive and prognostic marker of certain cardiovascular diseases and cancers (Katayama, Nakashima et al. 2005), (Morrow, Rifai et al. 2000), (Johnson, Kip et al. 2004), (Malle, Sodin-Semrl et al. 2009). SAA is used routinely in veterinary sciences (Murata, Shimada et al. 2004), and also plays a role as a major APP in mice, which enables the use of mouse models.

### 1.2 Moderate APPs

The concentrations of most **moderate** APPs begin elevating at 24-48 hours following the APR and peaking at 2-5-fold of their physiological levels. Following a 7-14 day period they return to physiological levels. Some examples of moderate APPs are  $\alpha$ 1-acid glycoprotein/orosomucoid, haptoglobin, fibrinogen,  $\alpha$ 1-antichymotrypsin and  $\alpha$ 1-antitrypsin. Moderate APPs could play a vital function in APR, in providing support to the major CRP and SAA, and their roles, while at the same time playing distinct roles of their own such as protease inhibition, clot formation, limiting iron loss and acting as a steroid carrier.

### 1.3 Minor APPs

**Minor** APPs, such as ceruloplasmin, complement components C3 and C4, and ferritin increase their levels approximately 0.5-1-fold in the APR (Arnett, Edworthy et al. 1988; Mackiewicz, Kushner et al. 1993). However there are exceptions. In certain diseases, such as adult Still's disease (a rare systemic inflammatory disease of unknown etiology that is characterized by spiking high-fever usually exceeding 39°C, skin rash, and arthralgia), ferritin can increase to extremely high values (Schwarz-Eywill 1992, Jandus 2010).

### 1.4 Negative APPs

Interestingly, some APPs termed as **negative** APPs, lower their concentrations during the acute phase in the circulation. There is a multitude of negative APPs, such as transferrin, albumin, transerythrin/prealbumin, antithrombin. For example, albumin's serum levels decrease in order to stabilize oncotic pressure because of massive overproduction of the major positive APPs.

### 1.5 Functions of APPs

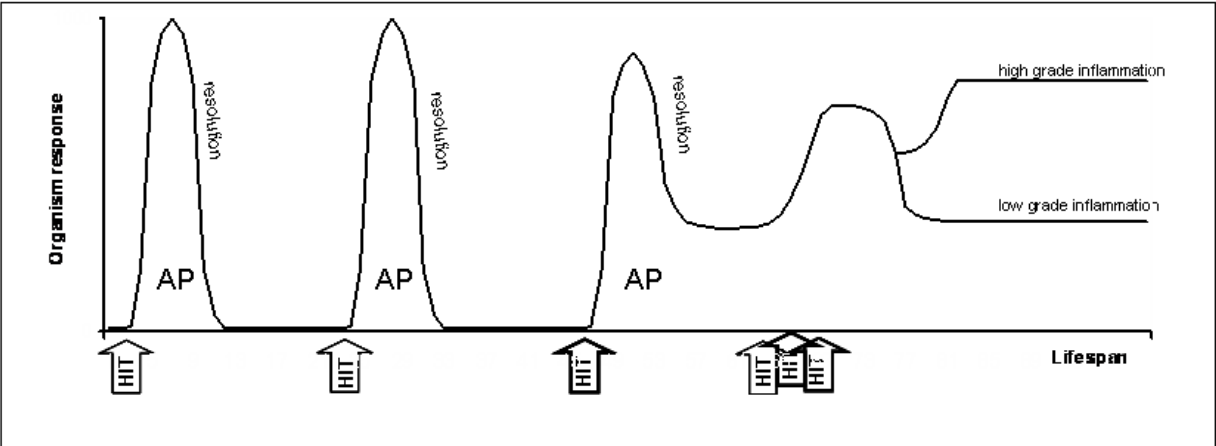
By function, APPs are involved in different processes (Table I), such as

- a. host defense (major APPs CRP and SAA, minor APPs such as C3, C4)
- b. wound healing role (with the major CRP and SAA having central roles and most other APPs playing multiple tasks)
- c. carrier/scavenger/transportation conserving vital substances, transport of metabolites/breakdown of cell debris, limiting available nutrients for bacterial growth, metal binding, antioxidant (ceruloplasmin, haptoglobin and transferrin)
- d. elimination of cell debris, opsonization (most notably CRP)
- e. protease inhibitors (moderate APPs such as  $\alpha$ 1-antichymotrypsin and  $\alpha$ 1-antitrypsin inhibit enzymes released from activated leukocytes and modulate cytokine activities)

f. blood clotting (such as fibrinogen and von Willebrand factor)  
APPs have also been previously divided into different types based on their regulators/stimulators yielding Type I APPs, which require both IL-1 and IL-6 synergistic stimulation for maximal production of CRP, SAA and  $\alpha$ 1-acid glycoprotein, and Type II APPs, which require only IL-6 for maximal synthesis (haptoglobin, fibrinogen, and others).

1.6 Time span of APP level changes leading to disease chronicity

In the lifespan of an organism the APR occurs immediately following hits (Scheme 1). This brings about highly elevated levels of major APPs, such as CRP and SAA in the circulation. Following repair mechanisms, the resolution (which can take anywhere from 3 to 14 days) of the APR gradually returns the APPs to baseline levels. During resolution it is thought that, among other processes, clearance of cell debris, opsonization and elimination of the large quantities of major APPs take place. There are postulations about how this complicated process can take place. Certain reports have indicated that antibodies against the major APPs might be involved (Arnett, Edworthy et al. 1988; Shoenfeld, Szyper-Kravitz et al. 2007; Lakota, Thallinger et al. 2011) in binding and clearing the mass quantities of APPs. These autoantibodies might act as natural antibodies involved in homeostasis.



Scheme Legend: **AP**; acute phase, **HIT**; represents injuries, infections, neoplasia and/or inflammation. During the lifespan of an organism acute phases occur following hits yielding high concentrations of major APPs, influx of inflammatory cells and higher production of inflammatory cytokines and chemokines to the site all acting in defense of the organism. The process is resolved through a complex mechanism yielding physiological levels of APPs. If, however, there are too many hits, leading to an acute phase which cannot be resolved, this may lead to irreversible chronicity with high, medium or low grade inflammation.

Scheme 1. Hypothetical patient’s outline of major APP level changes throughout his/her life, resolution phases and multiple hits leading to the irreversible vicious chronic inflammatory stage.

Whenever multiple hits occur simultaneously or consecutively in a short span of time or continuously throughout a longer span of time, recovery of the organism is no longer possible, nor is re-establishment of homeostasis. Throughout an organism’s lifetime (with aging and general senescence prevailing), the ability of establishing an APR, as well as that of returning to homeostasis becomes weakened/diminished. In healthy individuals multiple hits could lead to a less prominent APR, and in certain prone individuals, multiple hits

leading to the acute response could bring about a persistency of elevated APPs leading to chronic inflammation. In the absence of the resolution phase, a "domino effect" could occur, with APPs exerting long term degradative effects, specifically tissue and organ damage. Genetic predisposition of each individual plays a large role in determining if and when this happens. The challenge facing clinicians today is to treat patients early enough to prevent the irreversible cycle of chronicity, degradative tissue and organ damage. It is crucial to measure systemic markers in combination with monitoring local tissue and cell-specific changes "pre-chronically". Thus, longitudinal studies represent an important part for gathering data on early disease progression, however they are usually limited in time and number of patients.

### 1.7 Methodology description

Our report was limited to examples of rheumatic inflammatory diseases, patient population-based studies and APPs. Our initial search criteria included listing the specific "APPs" in the specific "disease" in PubMed and then narrowing the searches to patient population studies, human sera samples and protein levels (excluding genetic studies and mouse models). A division based on representative rheumatic inflammatory diseases, their disease stages, organ involvement (where applicable) and APPs (ordered by major, moderate, minor and negative APPs) has been selected in order to determine connections between them.

Table I has been constructed in order to give an overview and describe well-characterized APPs divided into groups (depending on their circulation concentrations during the acute phase) and their physiological levels during homeostasis along with potential and solely representative functions.

Only brief mention was given to the regulation of APPs, due to the complexity of different modulating molecules involved and their effects on APPs. Genetic predispositions and single nucleotide polymorphisms also largely fell outside the focus of this chapter. Understanding the mechanisms that modify APPs is an important step in developing new strategies in diagnosing and treating autoimmune diseases.

## 2. APPs indicating rheumatic disease pathology

The term "rheumatic diseases" comprises of a multitude (over 150) of different connective tissue diseases, syndromes, among them we have focused particularly on the most prevalent ones and characterized APPs in these diseases. Among the most noteworthy were: RA, ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS) and systemic vasculitis.

### 2.1 Rheumatoid arthritis (RA)

RA is a chronic systemic inflammatory autoimmune disease with prevalence of 0.8% (range 0.3–2.1%) of the population worldwide leading to severe disability and premature mortality. The most notable hallmark of RA is inflammation of the synovial joints, cartilage degradation and ultimately bone resorption, resulting in joint destruction. Secondary chronic inflammatory sites are also found in vessel walls resulting in accelerated atherosclerosis. As many as 40% of RA patients may have extraarticular manifestations, such as rheumatoid nodules, vasculitis, pleuropulmonary manifestations, pericarditis and (epi)scleritis. As a rule, these occur in patients with high titers of rheumatoid factor or antibodies against cyclic citrullinated peptides (anti-CCP) and are associated with increased



mortality as compared to other RA patients or age-matched control subjects. RA is associated with an increased incidence of lymphoma, especially large B cell lymphoma, particularly in patients with persistent inflammatory disease.

The 1987 American College of Rheumatology (ACR) classification criteria are useful for established RA, however are not sufficiently reliable when applied to patients with early RA (Arnett, Edworthy et al. 1988). In 2010 new RA Classification Criteria have been developed by ACR/European League Against Rheumatism Collaborative Initiative, focusing on identifying among patients newly presenting with undifferentiated inflammatory synovitis, factors that best discriminate between those who were and were not at high risk for persistent and/or erosive disease. Elevated APR defined by measuring erythrocyte sedimentation rate (ESR) and CRP levels is included in 2010 RA classification criteria as one of four scoring domains for classifying joint disease as definite RA (score  $\geq 6/10$ ) in patients with clinically confirmed synovitis of at least 1 joint and an absence of alternative diagnosis to explain synovitis.

## 2.2 Comparison of APPs in RA with healthy people and other diseases

In 66 patients with RA there was a significant elevation of CRP, ESR and von Willebrand factor above controls (Foster, Carruthers et al. 2010). SAA, apolipoprotein A, haptoglobin, ceruloplasmin were over-expressed when sera isolated from 6 RA patients and 6 healthy volunteers were screened and two-dimensional gel electrophoresis performed. ELISA confirmed that ceruloplasmin was expressed remarkably higher and the negative APP transthyretin was found to be under expressed in 32 RA patients as compared to the control group (Li, 2010). However, these differences were largely still within the normal range. Noe et al. (1995) found that 40% of 124 RA patients had an underlying iron deficiency (defined by ferritin values  $\leq 60$  ng/ml) (Noe, Augustin et al. 1995).

Surrall et al (1987, Clin Rheumatol) compared ceruloplasmin in RA, osteoarthritis, psoriatic arthritis and ceruloplasmin was significantly elevated in all disease groups (Surrall, Bird et al. 1987). Ceruloplasmin levels in 45 RA patients were significantly higher than in 50 osteoarthritic patients (Stojan and Hasler 1977). The same was shown in 32 RA patients as compared to 32 blood donors (Li, Zheng et al. 2010).

## 2.3 Comparison of different APPs in RA

A comprehensive study of 774 RA patients showed that CRP was an even better marker of disease activity than ESR (Wolfe 1997). There was good correlation also found between ESR, haptoglobin, fibrinogen, CRP, SAA and IL-6 in the serum ( $n=26$ ). They found especially strong correlations between CRP and SAA and between ESR and fibrinogen (Arvidsson, Gudbjornsson et al. 1998).

## 2.4 APPs in RA synovial fluid

In synovial fluid levels of ferritin, CRP and SAA were higher than serum levels in RA patients and correlated to degrees of joints inflammation in RA. Ferritin levels correlated with CRP and SAA in 34 synovial fluid samples but not in serum (Kumon, Suehiro et al. 1999).

## 2.5 APPs during RA disease stages

Acute phase reactants were included as one of the 3 most important variables, beside tender and swollen joint counts, in defining remission of RA at initial ACR/EULAR Consensus

Conference (van Tuyl, Vlad et al. 2009) and normal CRP and ESR levels are one of the three criteria defining disease inactivity in juvenile RA.

Patients with 25 very active RA had significantly higher SAA levels in the serum than 23 patients with moderately/mildly active or inactive disease (Maury, Teppo et al. 1982). SAA has been shown to correlate better with clinical markers of RA activity (as compared to ESR and/or CRP) (Hilliquin 1995). In over 120 patients with recent onset arthritis, very high levels of SAA occurred exclusively in 64 RA patients, as compared to psoriatic arthritis, undifferentiated arthritis and other forms of arthritis (Cunnane, Grehan et al. 2000). SAA might be the optimal systemic marker to test for early rheumatoid arthritis. Our group is currently involved in testing this hypothesis. Early RA (n=79) patients also had higher levels of von Willebrand factor, soluble intercellular adhesion molecule-1 and monocyte chemoattractant protein-1 as compared with controls (Sodergren, Karp et al. 2010).

Larsson et al. followed radiographic parameters in 200 patients with RA, which were correlated with laboratory parameters. CRP,  $\alpha$ 1-acid glycoprotein and haptoglobin showed a significant association with the severity and progression of radiographic parameters (Larsen 1988). Serum levels of  $\alpha$ -1 acid glycoprotein,  $\alpha$ -1 antichymotrypsin and antithrombin proteins in 25 RA patients were all higher at the onset of disease as compared with healthy controls. These decreased during the course of the disease and a positive correlation was shown with radiological progression (Lacki, Porawska et al. 1994). Markatseli et al. studied long-term clinical and radiological outcomes and predictive factors of radiological damage in RA at the 10-year follow up in a cohort of 144 northwestern Greek RA patients. Despite a significant clinical improvement, associated with a decrease of inflammatory markers along the timepoints, the radiologic progression of RA continued over time as defined with increased Larsen score and the number of erosive joints. Baseline radiographic damage (Larsen score and number of erosive joints), anti-CCP antibodies, and time-averaged levels of CRP constituted the main predictive factors of poor radiologic outcome in the long term (Markatseli, Voulgari et al. 2011). Lower expression of terminal sugars in synovial fibronectin was mainly associated with the early degenerative processes of RA. The higher expression levels of fibronectin terminal sugars could be associated with repair and adaptation processes. Such alterations may be applicable as a stage-specific marker for diagnosis and therapy of 58 RA patients (Przybysz, Maszczak et al. 2007).

Elevated fibrinogen levels have been observed in a number of inflammatory diseases, including RA and were shown to parallel RA disease activity assessed by DAS-28 and acute-phase markers ESR and CRP. In a study by Rooney et al. circulating fibrinogen levels were reported to be significantly higher in RA patients (n=105) compared to controls (n=62) and correlated positively and significantly with markers of inflammation (CRP, ESR, SAA, IL-6), composite and individual disease activity measures (DAS28-CRP/ESR, Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI)) (Rooney, Scherzer et al. 2011).

In RA patients, the value of serum  $\alpha$ 1-acid glycoprotein correlated with disease activity (Nakamura, Board et al. 1993). Both 35 men and 96 women with RA had increased  $\alpha$ 1-acid glycoprotein glycosylation (specifically fucosylation) as compared to healthy individuals in sera and synovia, which suggests a hepatic origin of synovial  $\alpha$ 1-acid glycoprotein as well (Havenaar, Dolhain et al. 1997). A weak correlation between  $\alpha$ 1-acid glycoprotein fucosylation and DAS28 was found only in 131 men (Ryden, Pahlsson et al. 2002), while Cylwik et al. reported that in 27 RA women  $\alpha$ 1-acid glycoprotein follows disease activity significantly, as do also CRP, transferrin, haptoglobin and  $\alpha$ 1-antitrypsin (Cylwik, Chrostek et al. 2010).

Serum  $\alpha$ -1 antichymotrypsin concentrations were confirmed to be significantly elevated in 47 RA patients (Kosaka and Tazawa 1976) and reflected disease activity in 20 RA patients (Chard, Calvin et al. 1988).

Although hypocomplementemia is likely to occur in immune complex-mediated diseases such as RA, increases in C3, C4, C5a occur in active disease (Low and Moore 2005). The study that showed anti-CCP concentrations to be positively correlated to C3 levels in anti-CCP positive was performed in 123 RA patients (Xun and Zhao 2011). Complement activation was shown to be mediated via anti-CCP, as well as via CRP in RA. Elevated split products of C3, C4 were found in many associated studies in RA patients with C9 being more consistently elevated in active disease than CRP or ESR (Rumfeld, Morgan et al. 1986).

A limited retrospective study of RA patients found that serum levels of secreted phospholipase A2 activity correlated with disease activity (Pruzanski, Keystone et al. 1988). To assess the strength of this relationship the group investigated prospectively 212 patients with RA using a double blind approach. 65 patients were assessed on one occasion and 147 on multiple occasions (a mean of 2.41 visits/patient). Serum secreted phospholipase A2 activity was confirmed to correlate with disease activity in this expanded study, and secreted phospholipase A2 activity was shown to significantly correlate with the Lansbury index, active and effused joints, ESR, platelet count, and hemoglobin (Lin, Farewell et al. 1996). Antithrombin-III levels were significantly increased in RA. Antithrombin-III depended upon disease activity and duration (from 25 to 44% patients with increased levels) (Zorina, Zorina et al. 2008).

Two other studies in 2009 measured ferritin levels and reported lower levels of serum ferritin in 61 RA patients with anti-CCP antibodies (Onder et al., 2009) or unchanged serum ferritin levels in 30 RA patients or with disease activity (Pallinti et al., 2009).

The levels of negative APPs decrease during the APR, while in disease states this can be significantly modulated. Helliwell et al. showed in 1984, that transerythrin was significantly decreased in the 54 RA patients with little relationship to disease activity as assessed clinically. RA patients with reduced transerythrin had an increased frequency of associated anthropometric and serum visceral protein abnormalities indicating nutritional impairment (Helliwell, Coombes et al. 1984).

Interestingly, increased serum levels of the negative APP leucin rich- $\alpha$ 2-glycoprotein were identified by proteomic analysis of 326 proteins in RA patients prior to therapy. Serum leucin rich- $\alpha$ 2-glycoprotein concentrations were significantly elevated in RA patients as compared to healthy controls and decreased after anti-tumour necrosis factor therapy. Furthermore, serum leucin rich- $\alpha$ 2-glycoprotein concentrations correlated with disease activity in RA (Serada, Fujimoto et al. 2010).

## 2.6 APPs and RA vascular involvement

There was an inverse correlation reported between serum levels of SAA and reduced small artery and large artery elasticity in 52 patients (Wong, Toh et al. 2003). These correlations could be clinically important in detecting, monitoring and predicting vascular disease in RA. The hyperproduction of von Willebrand factor antigen was found to be associated with skin vasculitis symptoms in 43 RA patients (Baranov, Shilkina et al. 1993).

As shown for hs-CRP, compared to controls, fibrinogen levels remained significantly elevated even in RA patients with no joint disease activity and the degree of fibrinogen elevation was consistent with a significant contribution to cardiovascular disease risk (1.8-fold increase). This is important as fibrinogen predicts coronary heart disease independently



of inflammatory markers and cardiovascular disease is now widely accepted as the leading cause of death in RA (Rooney, Scherzer et al. 2011).

A study found a higher prevalence of atherosclerosis in RA patients, with von Willebrand factor serum levels significantly elevated in 66 of these patients as compared to control patients and von Willebrand factor levels correlated with intima media thickness of the left common carotid artery in 55 of the RA patients (Daza, Aguirre et al. 2007). Several studies have reported that lipoprotein (a) also associates with early atherosclerosis in RA. Significantly higher lipoprotein (a) values were found in RA patients than in controls (n=184 patients (Yoo 2004), n=87 patients (Dursunoglu, Evrengul et al. 2005), n=122 patients (Garcia-Gomez, Nolla et al. 2009)), while one study in 69 RA patients and 491 controls did not confirm this finding (Solomon, Curhan et al. 2004). Lipoprotein (a) concentrations in active RA were higher than those in both inactive RA and controls as measured in 54 RA patients (Wang, Hu et al. 2008).

### 3. Spondyloarthropaties (SpA)

SpA patients are characterized by axial and peripheral arthritis, associated with enthesitis, dactylitis and extra-articular manifestations such as uveitis and skin rash (Ehrenfeld, Shoenfeld et al. 2008).

Ankylosing spondylitis (AS), a prototypic form of spondyloarthritis, is a chronic systemic inflammatory disorder affecting mainly the axial skeleton (spondylitis) and sacroiliac joints (sacroiliitis) and shows significant inherited susceptibility. Arthritis of peripheral joints, usually asymmetric, occurs in up to 30% patients and acute anterior uveitis is the most common extraarticular manifestation. In AS, the entheses are affected, with inflammation (enthesitis), bone destruction and syndesmophyte formation being principal disease mechanisms, resulting in ankylosis of spine and considerable disability. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) are clinical scores used to assess disease activity. A new activity index, Ankylosing Spondylitis Disease Activity Score (ASDAS) also considers ESR and CRP as biomarkers. Novel promising candidates are emerging such as SAA, matrix metalloproteinase 3, type II collagen neoepitopes, c-propeptide of type II collagen, aggrecan 846 epitope, macrophage colony stimulating factor and IL-6, among others (Romero-Sanchez, Londono et al. 2010).

In 72 AS patients, there were two valuable surrogate markers of disease activity, namely ESR and CRP, and an established clinical activity score (BASDAI). Serum levels of SAA were correlated to CRP, ESR and BASDAI in AS patients (Lange, Boss et al. 2000). The same was later confirmed with 38 AS patients (Jung, Park et al. 2007). Elevated baseline CRP and SAA levels revealed the highest predictive value for responsiveness to anti-TNF $\alpha$  treatment in 155 AS patients (de Vries, van Eijk et al. 2009). Among many measured APP values only  $\alpha$ 1-antitrypsin was shown to be significantly lower in remission or partial remission group (Ozgocmen, Godekmerdan et al. 2007). SAA, apolipoprotein A-IV and its precursor, haptoglobin, ceruloplasmin and immunoglobulin superfamily 22 were all consistently over-expressed by more than 3-fold in the sera of AS patients as compared to healthy volunteers. This study used two-dimensional electrophoresis in combination with mass spectrometry to search for disease-associated proteins in the sera of 6 AS patients (Li, Zheng et al. 2010).

In 1989, a comprehensive study tested sera from 45 patients with AS for correlation of serum IgA and six APPs: CRP,  $\alpha$ 1-antitrypsin,  $\alpha$ 1-antichymotrypsin, ceruloplasmin,  $\alpha$ 1-acid

glycoprotein and haptoglobin. Serum IgA significantly positively correlated with CRP,  $\alpha$ 1-antitrypsin,  $\alpha$ 1-acid glycoprotein, and haptoglobin, suggesting that gastrointestinal immunostimulation plays a role in the pathogenesis of inflammation in AS. Since microheterogeneity in glycosylation was found reactivity of  $\alpha$ 1-acid glycoprotein with concavalin A was used for measuring this modification and coefficient of reactive variants versus nonreactive was calculated. In AS patients,  $\alpha$ 1-acid glycoprotein reactivity coefficient was significantly decreased as compared to healthy controls, while increasing in infection, remaining the same in SLE, and decreasing in RA (Mackiewicz, Khan et al. 1989).

Ankylosing spondylarthritis has been associated with haptoglobin 2-2 subtype (Soliev, Arifzhanov et al. 2002). In sera of AS analyzed by ESI-Q-TOF MS/MS highly expressed isoforms of haptoglobin precursor were found. Bioinformatic analysis revealed epitopes derived from haptoglobin precursor with high affinity binding to HLA-B(\*)2705, a primary subtype associated with AS. These indicate that haptoglobin precursor might be involved in the pathogenesis of AS (Liu, Zhu et al. 2007).

In addition to AS, there have been reports of APP studies found in psoriatic arthritic and enteropathic SpA patients. Higher values of ceruloplasmin were demonstrated in 45 psoriatic arthritis sera as compared to 63 psoriasis sera alone or 60 healthy individuals (Oriente, Scarpa et al. 1984) with the number of synovial joints affected, significantly correlating to changes in this serum parameter.

Plasma levels of fibronectin and two spliced isoforms, Ed-A and Ed-B, in 10 patients with SpA showed an increase in plasma levels of fibronectin and Ed-B fibronectin as compared with 10 RA patients and 21 healthy volunteers, which could not be attributed solely to systemic inflammation. No significant correlation was observed in SpA patients between fibronectin level and clinical activity, ESR or CRP levels. (Claudepierre, Allanore et al. 1999). Following colonoscopy, 38 undifferentiated SpA patients all had microscopic inflammatory lesions which were clinically silent. Direct immunofluorescence demonstrated the presence of C3, C4 and fibrinogen in 75% of the specimens examined and it was suggested that local activation of the immune system due to intestinal microbial antigens or toxins, with impaired elimination or increased exposition, may have a part in the pathogenesis of SpA (Altomonte, Zoli et al. 1994).

#### 4. Systemic lupus erythematosus (SLE)

SLE is a prototype of a chronic systemic autoimmune disease with multiple organ involvement and the presence of antinuclear autoantibodies. SLE is characterized by a variety of clinical/laboratory abnormalities, such as fever, arthritis, rash, nephritis, neurological disease, serositis, alopecia, leucopenia and thrombocytopenia. The course of disease is characterized by exacerbations – flares interspersed with periods of relative remission but permanent complete remission is rare. Systemic symptoms, particularly fatigue and myalgias/artralgias are present most of the time. Nephritis is the most serious manifestation, being along with infections the leading cause of mortality in the first decade of disease. Worsening of characteristic butterfly rash often accompanies a flare of a systemic disease. SLE is associated with an increased risk of myocardial infarction due to accelerated atherosclerosis (which probably results from chronic inflammation/ oxidative damage) but also the presence of antiphospholipid antibodies. The diagnosis of SLE is based on characteristic clinical features ( $\geq 4$  out of 11 diagnostic criteria for SLE) and the presence of autoantibodies with antinuclear antibodies being diagnostically most important (positive in

>95% of patients). Anti-dsDNA and anti-Sm antibodies are specific for SLE and an increase in anti-dsDNA antibody titers may herald a flare, particularly of nephritis or vasculitis. There is a great interest toward identifying new additional markers of SLE activity or its response to therapy among them complement proteins, interferon gamma-inducible genes, soluble interleukin 2 and urinary adiponectin or monocyte chemotactic protein 1. The APR in SLE is not very pronounced or is even suppressed (Bertouch, 1983), as represented by low CRP values which have no implication in diagnostic procedure. In contrast to CRP, SAA, the second major APP, is significantly higher in SLE (n=109 patients) than in the control group (n=78 (Rho, Chung et al. 2008); n=42 (Esmat, El-Sherif et al. 2005), n=26 (Lakota, Thallinger et al. 2011)). Raised SAA concentrations may indicate disease activity, as well as lupus nephritis in SLE, but cannot be used for monitoring responses in patients on systemic corticosteroid therapy.

#### 4.1 Possible mechanisms of low APR response

The potential nonresponsiveness of certain APPs (specifically CRP,  $\alpha$ 1-acid glycoprotein and  $\alpha$ 1-antichymotrypsin) to cytokine (IL-1, IL-10, TNF- $\alpha$ , IL-6) stimulation has been proposed and the results suggest a rare independence of APPs from cytokine regulation in most instances of this disease ((Gabay, Roux-Lombard et al. 1993); (Lacki, Samborski et al. 1997)). However in one report, both IL-10, as well as  $\alpha$ 1-acid glycoprotein, were found to be significantly elevated in SLE. Since IL-10 has potent immunosuppressive characteristics, it was surprising that it did not negatively correlate with APPs. Based on the obtained data, the group suggested that IL-10 may play a central role in inflammatory connective tissue diseases (Lacki, Samborski et al. 1997). Additionally the attempt to address the question of why CRP is not elevated overall in SLE, Liou et al. (2003) proposed that SLE has two types of monocytes responding either to lipopolysaccharides or immune complexes, while in RA monocytes respond to both stimuli (Liou 2003). Many studies were conducted in order to determine whether anti-CRP antibodies are responsible for the low CRP. They concluded that there was no correlation between anti-CRP antibodies with their CRP antigen in sera of SLE patients and this, in combination with no fluid phase inhibition, leads one to suspect an unlikely role of antibodies involved in the clearance of native antigen, with autoantibody titer following SLE activity (reviewed in (Sjowall and Wettero 2007)). With the availability of high-sensitivity assays for CRP, its detection can become more evident in certain cases of SLE.

#### 4.2 Comparison of APPs with healthy controls, and other diseases

Ruiz-Argüelles et al. (1991) reported that plasminogen activator inhibitor type 1 had abnormally high concentrations, with fibrinogen and plasminogen levels also significantly elevated in 18 SLE patients than in normal controls, even though both the latter were generally within normal range (Ruiz-Argüelles, Ruiz-Argüelles et al. 1991). Significantly raised  $\alpha$ 1-acid glycoprotein levels were measured in all clinical periods in three SLE patients in 19 clinical periods. There was no association found between significantly raised  $\alpha$ 1-acid glycoprotein levels in SLE and TNF- $\alpha$  and IL-6, or between TNF- $\alpha$ , IL-6 and levels of CRP and  $\alpha$ 1-acid glycoprotein. These data could not be explained by changes in disease course or therapy influences. It was concluded that other factors (other than TNF- $\alpha$  and IL-6) may play a role in the regulatory pathway of the APR in SLE (Meijer, Huysen et al. 1993).

Mannose-binding lectin, the protein responsible for activation of complement through lectin pathway levels was reported to be higher in SLE patients sera (Schafranski, Stier et al. 2004), (Scalzi, Hadi et al. 2010) on contrary low levels of mannose-binding lectin predispose patients to various infectious and inflammatory disorders and have been reported to be associated with idiopathic recurrent early and late miscarriages (Christiansen, Nielsen et al. 2009) which can also be seen in SLE.

Surrall et al (1987, Clin Rheumatol) studied ceruloplasmin in SLE and found that, contrary to RA, ceruloplasmin was not found to be significantly elevated in this disease (Surrall, Bird et al. 1987).

Alpha2-HS-glycoprotein is a negative APP and is a human homologue of the carrier protein fetuin-A. Serum  $\alpha$ 2-HS-glycoprotein concentrations in 63 SLE patients were determined, and found to be significantly lower as compared to those of 59 healthy blood donors (Kalabay, Jakab et al. 1990).

#### 4.3 APPs during SLE disease stages

Spronk et al. (1992) studied 16 SLE cases with disease exacerbation. CRP levels were elevated in isolated cases, dependently upon higher IL-6 levels (which occurred mainly in serositis) (Spronk, Limburg et al. 1995). This was confirmed in a report where CRP was recently proposed as a therapeutical agent in lupus and also, as a biomarker in order to distinguish between SLE with and without serositis (de Carvalho, Hanaoka et al. 2007).

Increased fibrinogen levels were observed in 35% of 115 SLE patients without relating to disease activity (Beyan, Beyan et al. 2007). Plasma levels of von Willebrand factor were elevated in SLE patients (n=40 (Curiel, Bhagati et al. 2008), n=36 (Mannucci, Vanoli et al. 2003)) and in these, the degree of red blood cell fragmentation correlated with lupus disease activity over time. Therefore, inflammation in SLE is likely to be associated with endothelial injury (Curiel, Bhagati et al. 2008).

Ferritin is a storage protein for iron and its serum levels were found to correlate with higher disease activity scores (with higher >10 SLE disease activity index (SLEDAI)), than in SLE patients with lower disease activity. Changes in SLEDAI scores before and after treatment positively and significantly correlated with serum ferritin levels and inversely to C3 and C4 levels (n=128 (Lim, Lee et al. 2001), n=72, (Beyan, Beyan et al. 2003), n=36 (Nishiya and Hashimoto 1997)), which have also been reported to be useful for measuring SLE activity (Spronk, Limburg et al. 1995). Hyperferritinemia was detected in 23% of 138 SLE patients (Orbach, Zandman-Goddart et al. 2007) On the other hand, there was also study reporting high increase in some cases and no increases in others in ferritin levels during flares (follow up 10 SLE patients, 4,8 years ) (Hesselink, Aarden et al. 2003).

Fibronectin levels in patients with active SLE were significantly higher than in patients with non-active SLE or in normal subjects (Nishinarita, Yamamoto et al. 1990).

#### 4.4 APPs and SLE organ involvement

Sturfelt et al. (1984) reported on 33 SLE patients who were assigned to three groups representing mild SLE, more severe or extrarenal SLE, and SLE with significant renal involvement. In patients with extrarenal disease, the inflammatory plasma protein response was often pronounced during exacerbation, as evidenced by markedly increased concentrations of CRP,  $\alpha$ 1-antichymotrypsin,  $\alpha$ 1-antitrypsin, and  $\alpha$ 1-acid glycoprotein. CRP responses were rare in patients with renal involvement, despite the increased concentrations of other acute-phase reactants in some of these patients (Sturfelt and Sjöholm 1984).



In 98 lupus nephritis pediatric patients and 30 juvenile idiopathic arthritis, urinary acute phase biomarkers were evaluated including transferrin, ceruloplasmin,  $\alpha$ 1-acid glycoprotein and albumin. All tested urinary proteins were significantly higher in active vs. inactive lupus nephritis or no lupus nephritis. Significant increases of urinary transferrin and  $\alpha$ 1-acid glycoprotein occurred as early as 3 months before the clinical diagnosis of worsening lupus nephritis, indicating that these proteins are biomarkers of lupus nephritis activity and may help anticipate the future course of lupus nephritis (Suzuki, Wiers et al. 2009).

C3, C4 levels in active SLE or renal/extrarenal involvement have been studied with contradicting results and are reviewed by Liu (Liu, Ahearn et al. 2004). Hypocomplementemia was detected in 62% SLE patients (n=597) and showed a higher prevalence of female gender, fever, nephropathy, cutaneous vasculitis, positive anti-dsDNA antibodies and cryoglobulinemia, a higher prevalence of antiphospholipid syndrome-related features such as hemolytic anemia and antiphospholipid antibodies, but not with the accumulated number of lupus flares or with the survival after a five year follow-up (Ramos-Casals, Campoamor et al. 2004). In contrast, a study of 605 SLE patients reported C3 to be increased and associated with carotid plaques (Maksimowicz-McKinnon, Magder et al. 2006). The complex of immunoglobulin A and  $\alpha$ 1-antitrypsin was found to be elevated in a number of rheumatic diseases. In 50% of SLE and RA patients the levels of complex are increased, strikingly and especially in those with current central nervous system involvement. Their presence correlates with the progression of the disease (Lacki, Schochat et al. 1995).

Fibrinogen in 96 SLE patients median baseline levels were higher than in 39 controls, particularly in patients with thromboses and in patients with longer disease duration as compared to other patient groups. Plasma fibrinogen increases in patients with SLE throughout follow-ups regardless of disease activity, mimicking age-related increments observed in population-based studies. The rapidity of the increment may reflect the prematurity of vascular disease typical of SLE (Ames, Alves et al. 2000). Hyperfibrinogenemia was more common in patients with skin/mucosal involvements in 115 SLE patients (Beyan, Beyan et al. 2007).

Antithrombin, protein C and protein S, natural anticoagulants, weren't significantly changed in SLE patients (Tomas, Alberca et al. 1998) and are independent of a history of thrombosis, however their levels could change in patients using prednisone (Costallat, Ribeiro et al. 1998). This is confirmed with a study by Afeltra et al. (2005) which reported that antithrombin, protein C and fibrinogen were all found to be significantly higher in 57 SLE patients, all of whom were receiving prednisone, however they did not find any correlations with thromboses (Afeltra, Vadacca et al. 2005).

Atherosclerosis is known to be accelerated in long-term well-controlled SLE. SAA was significantly increased in pre - and post-menopausal SLE patients and intima-media thickness was found to be associated with increased SAA in pre-menopausal SLE patients (Sato, Miida et al. 2007).

Osteonecrosis was significantly associated with elevated levels of plasminogen activator inhibitor type 1 activity in 26 SLE patients which causes imbalance between protein and its inhibitor (Sheikh, Retzinger et al. 1998).

## 5. Primary Sjogren's syndrome (pSS)

Primary Sjögren's syndrome is a chronic autoimmune disease characterized by enlargement of the major salivary glands (e.g parotid gland), xerostomia and *keratoconjunctivitis sicca*.



Salivary glands are infiltrated in more than two thirds of patients with CD4+ T cells which produce inflammatory cytokines while other exocrine glands are involved less frequently. Extraglandular (systemic) manifestations, such as arthralgias/arthritis, Raynaud's phenomenon, lymphadenopathy, lung, kidney or liver involvement and vasculitis are present in one-third of patients. Autoantibodies directed against Ro/SS-A and La/SS-B antigens, are often present usually at the time of diagnosis and associated with earlier disease onset, longer duration, salivary gland enlargement, more severe lymphocytic infiltration of minor salivary glands, and certain extraglandular manifestations. The high ESR and highly expressed dysproteinemia are the hallmarks of disease but without any valuable influence on disease diagnosis. Malignant lymphoma, mostly extranodal, low-grade marginal zone B cell lymphoma, is a well-known manifestation with incidence of 6%, usually presenting later in the disease. Persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinemia, and low C4 complement levels suggest the development of lymphoma and are associated with increased mortality.

In the early 1980s it was pointed out that CRP is usually low in patients with pSS (Moutsopoulos, HM 1983). Recently, only modestly elevated CRP levels were found in 74 pSS patients (Pertovaara, Jylhava et al. 2009). Levels of SAA are increased in 74 patients with pSS as compared to 56 controls and immunological markers in patients with pSS are associated with variation in SAA levels. In pSS patients, SAA concentrations correlated significantly with age, leukocyte count, CRP, interleukin 6, and C4. Unlike CRP, there was a significant inverse correlation between SAA and serum IgG levels and anti-ribonucleoprotein SSA antibody titers, as well as a trend towards an inverse correlation between SAA and antinuclear antibody and rheumatoid factor titers. This implies that high SAA production could constitute a protective element in pSS with explanation that high SAA levels inhibit in particular various signs of B cell hyperreactivity, i.e., IgG and autoantibody production. SAA levels were significantly higher in pSS patients with myalgic symptoms as compared to those without, and in patients with neurological symptoms as compared to those without. However, median SAA levels did not differ significantly between patients with pSS and subjects with nonimmunologically-derived sicca symptoms. A subgroup of patients suffering from pSS displayed unexplainably low levels of complement components C3 and/or C4 which were associated with an increased risk of non-Hodgkin's lymphoma (Pertovaara, Jylhava et al. 2009).

## **6. Systemic vasculitis**

Vasculitis is a generalized inflammation of blood vessels with numerous polymorphonuclear cells in acute lesions and lymphocytes in chronic lesions. Inflammation affects different layers of vessels and resolves usually with fibrosis and hypertrophy. Most immediate damage occurs when inflammation narrows arteries, forms clots which all cause tissue ischemia and necrosis. Systemic vasculitis spans from autoimmune diseases to nonautoimmune disorders affecting different vascular compartments by size and leading to a multitude of different subcategories some of them presented in this chapter. ESR and CRP are usually significantly elevated, however serve as nonspecific markers for systemic vasculitis.

### **6.1 Polymyalgia rheumatica and giant-cell arteritis**

Polymyalgia rheumatica and giant cell arteritis are closely associated disorders and may represent differing clinical spectrums of a single disease process. Polymyalgia rheumatica is

characterized by stiffness and pain in the proximal muscles and most commonly occurs in isolation, but may be seen in 40–50% of patients with giant cell arteritis. In polymyalgia rheumatica, SAA levels were more sensitive and always elevated in determining disease activity as compared to CRP or ESR measurements which stayed at baseline levels (Hachulla, Saile et al. 1991). In addition, in polymyalgia rheumatica patients despite glucocorticoid treatment, the levels of only some APPs fell below the initial measurements at the outbreak of disease (CRP, haptoglobin,  $\alpha$ 1-acid glycoprotein, fibrinogen), while plasminogen activator inhibitor type 1 and von Willebrand factor stayed increased despite clinical remission (Uddhammar, Rantapaa-Dahlqvist et al. 1992).

Giant cell arteritis, is a systemic vasculitis, affecting medium- and large-sized arteries, most offently one or more branches of the carotid artery, particularly the temporal artery (cranial or temporal arteritis). It is characterized by fever, high ESR, anemia and headaches in a patient over 50 years with most dreaded complication being an ischemic optic neuropathy. Giant-cell arteritis frequently posses diagnostic and therapeutic challenges. Although the ESR, CRP and platelet count continue to be the primary markers, others, such as interleukin-6 and fibrinogen can provide additional information (Hall 2008). Not all patients with giant cell arteritis had increased levels of CRP, haptoglobin and fibrinogen (Gudmundsson, Nordborg et al. 1993), but CRP and fibrinogen levels fell to normal levels quickest after starting glucocorticoid treatment (67% patients in two weeks), while ESR followed later and haptoglobin being the slowest (Andersson, Malmvall et al. 1986). In contrast to CRP and ESR, which lowered after prednisolone treatment,  $\alpha$  1-antichymotrypsin may be useful as an indicator of underlying disease activity (Pountain, Calvin et al. 1994). A prospective clinical study on 23 patients with giant-cell arteritis concluded that SAA measurements are more sensitive than CRP in determining disease activity. The specificity of SAA was greater than ESR in the determination of inactive disease. In some cases in clinically active disease, ESR and CRP were normal, whereas SAA was always elevated, so SAA measurements in combination with clinical data and other laboratory parameters could be useful in the management of giant-cell arteritis (Hachulla, Saile et al. 1991).

## 6.2 Takayasu arteritis

Takayasu's arteritis is an inflammatory and stenotic arterial disease (panarteritis) involving medium- and large-sized arteries with a strong predilection for the aortic arch and its branches. It affects mainly young women with an estimated annual incidence rate of 1.2–2.6 cases per million. Plasma of acute and chronic Takayasu's arteritis and healthy people, each consisting of 20 individuals were investigated for differential expression using two-dimensional electrophoresis, mass spectrometry, and circulating levels were then determined by enzyme immunosorbent assay. Levels of SAA and C4 binding protein were significantly increased (Luo, Wu et al. 2010). In a similar study, SAA and C4 binding protein were significantly elevated in 43 active Takayasu arteritis patients as compared to nonactive patients and controls, among all other APPs measured, including CRP (Ma, Luo et al. 2010).

## 6.3 Kawasaki disease

Kawasaki disease, an acute, febrile, mucocutaneous lymph node syndrome, of children, can be complicated with vasculitis of the coronary arteries, resulting in coronary artery aneurysms. In Kawasaki disease, SAA is significantly elevated (Cabana, Gidding et al. 1997). There was association found between both elevated SAA and CRP and the persistence of coronary sequelae late after Kawasaki disease, associated with coronary vascular events

(Mitani, Sawada et al. 2005). Haptoglobin genotype significantly influenced the presentation of clinical signs of Kawasaki disease with haptoglobin 2-1 allele patients having delayed or incomplete presentation of clinical symptoms of 47 patients with Kawasaki disease (Lee, Hwang et al. 2000). In attempt to distinguish Kawasaki disease from other febrile illnesses sera from 218 children were analyzed (among them, 64 with Kawasaki disease, and other children with diseases such as bacterial pneumonia, upper respiratory tract infection and others). Haptoglobin/apolipoprotein A-I ratio were significantly higher for the Kawasaki disease patients than the rest and with cut-off ratio of 2, with a sensitivity of 89.7% and a specificity of 85.6% for detecting Kawasaki disease (Huang, Gupta-Malhotra et al. 2010).

The proteome profiling of Kawasaki disease serum on 2D-PAGE and ELISA showed higher fibrinogen-related proteins (fibrinogen,  $\alpha$ 1-antitrypsin, clusterin, and CD5L), along with a lower level of the immunoglobulin free light chains that involve fibrin degradation in Kawasaki disease. This unique proteomic profiling with abnormal fibrinogen cascade may provide a good biomarker of Kawasaki disease and a better strategy to prevent cardiovascular complications of Kawasaki disease by correcting abnormal fibrin deposition or degradation (Yu, Kuo et al. 2009). In 36 Kawasaki disease children plasma fibrinogen levels in patients with coronary artery lesions were significantly higher than those in patients without coronary artery lesions or in the control group (Gao, Wang et al. 2010).

Predictive factors of coronary aneurysm in Kawasaki disease were reported to be multiple APPs, with special emphasis on the correlation between coronary arterial lesions and serum albumin, prealbumin, retinol-binding protein and immature neutrophils (Nakano 1987).

## 7. Behçet's disease

Behçet's disease, a systemic perivasculitis, is characterized by recurrent oral and genital ulcerations as well as ocular involvement (iritis, posterior uveitis, panuveitis). Differentially expressed proteins were searched for in the serum of Behçet's disease. SAA and haptoglobin were determined to be significantly increased by MALDI-TOF/TOF MS in sera of active Behçet's disease, with haptoglobin only in active Behçet's disease and SAA in 72% of all Behçet's disease and 10% of controls (Mao, Dong et al. 2008). A more recent study found higher haptoglobin levels in patients with Behçet's as compared to healthy controls, but no differences in active/nonactive uveitis among the Behçet's disease patients (Yalcindag, Yalcindag et al. 2008). A report of 33 patients with Behçet's disease indicated that patients with active Behçet's disease had higher ESR, CRP and lipoprotein (a) levels, and lower apolipoprotein A and high density lipoprotein-C levels as compared to patients with inactive Behçet's disease and healthy controls (Musabak, Baylan et al. 2005).

Similarly, plasma lipoprotein (a) and CRP concentrations were significantly higher in the study group than in the controls. These concentrations were also higher during the active period of the disease than during the inactive phase. Lipoprotein (a) concentrations were significantly correlated with concentrations of other acute phase reactants, however there was a suggestion that plasma levels of lipoprotein (a) might be an indicator of disease activity in Behçet's disease. No difference was found between the groups with and without thrombotic complications for any of these measurements. There is no correlation between lipoprotein (a) levels and thrombotic sequela in inactive Behçet's disease (Gurbuz, Ozdemir et al. 2001).

APP groups during APR (Fold increase/decrease)	Name	Concentration in homeostasis (mg/l) unless otherwise stated	Representative Function/s
Major APP, >5-fold increase	Serum amyloid A	<10 <sup>1</sup>	Cytokine-like, chemoattractant, induction of matrix metalloproteinases, adhesion molecules, lipid metabolism
	C-reactive protein	<5 <sup>1</sup>	Opsonization
Moderate APP, ~2-5 fold increase	Haptoglobin	400-1800 <sup>1</sup>	Binds hemoglobin, limits iron loss
	α1-Acid glycoprotein	400-1050 <sup>2</sup>	Carrier of lipophilic components, steroid carrier, immunosuppressive for lymphocytes
	Mannose binding lectin	1.4 (±0.4) <sup>3</sup>	Pathogen recognition molecule, opsonising microorganisms, initiating the complement cascade
	α1-Antichymotrypsin	300-1600 <sup>1</sup>	Protease inhibitor
	α1-Antitrypsin	2000-4000 <sup>2</sup>	Protease inhibitor, induction of cell proliferation, synthesis of collagen, chemoattractant
	Fibrinogen	1000-4000 <sup>2</sup>	Clot formation
	Secretory phospholipase A2	15.1-32.1 U/ml <sup>4</sup>	Increases expression of inflammatory cytokines, associates with lipoprotein
	Fibronectin	234 (±21) <sup>5</sup>	Binds to extracellular matrix and integrins, important in cell adhesion, migration, wound healing, forms immune complex with C1q, fibrin clot formation
	von Willebrand factor	107 U/dl <sup>6</sup>	Marker of endothelial injury/activation coagulation protein, role in collagen binding, platelet glycoprotein Ib binding, and factor VIII stabilization.
	Plasminogen activator inhibitor-1	47.1 (±4.6) ng/ml <sup>7</sup>	Principal inhibitor of fibrinolysis (Inhibitor of plasminogen activators and plasmin production), serine protease inhibitor
	Lipoprotein (a)	11.1-78.1 mg/dl <sup>8</sup>	Atherosclerogenic and thrombogenic plasma protein
Minor APP, increases ~0.5-fold	Ceruloplasmin	200-400 <sup>2</sup>	Cu <sup>2+</sup> binding, oxidation of Fe <sup>2+</sup>
	Complement component 3	600-1400 <sup>2</sup>	Opsonization (chemotaxis)
	Complement component 4	150-650 <sup>1</sup>	Opsonization
	Ferritin	12-300 µg/l <sup>2</sup> higher in men	Oxidizes Fe <sup>2+</sup> , stores Fe <sup>3+</sup>
Negative APP, decreases	Transferrin	1,17-2,5g/l <sup>2</sup>	Iron binding
	Transerythrin	0,2-0,4g/l <sup>2</sup>	Retinol binding protein and thyroxin
	Antithrombin	0.15 g/l <sup>9</sup>	Inhibition of coagulation enzymes, which is potentiated by heparin

Legend: Table 1. bibliography:  
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<sup>2</sup> McPherson, R. A.Pincus, M. R. (2007). Henry's Clinical Diagnosis and Management by Laboratory Methods (21), Saunders Elsevier, ISBN 978-1-4160-0287-1, PA, USA

<sup>3</sup> Olivier Van Till, J.W. et al. (2006). Variable Mannose-Binding Lectin Expression during Postoperative Acute-Phase Response. Surgical Infections 7(5), 443-452. doi:10.1089/sur.2006.7.443.

<sup>4</sup> Lima, L.M. et al. (2010). Secretory phospholipase A2 in patients with coronary artery disease. J Thromb Thrombolysis 29(3), 276-81.

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<sup>7</sup> Collet, J.P. et al. (2003). Acute release of plasminogen activator inhibitor-1 in ST-segment elevation myocardial infarction predicts mortality. Circulation 108(4):391-4.

<sup>8</sup> Karatay, S. et al. (2010). Increased serum concentrations of homocysteine and lipoprotein (a) in familial Mediterranean fever. Ann Clin Lab Sci 40(1):10-4.

<sup>9</sup> Conard J. et al. (1983). Molar antithrombin concentration in normal human plasma. Haemostasis 13(6):363-8.

Table 1. Overview of selected APPs, their typical homeostatic concentrations and representative functions

Acute phase C9 was a sensitive index of disease activity; however, it failed to discriminate between the three types of recurrent oral ulcers and four types of Behçet's disease. The level of  $\alpha$ 1-acid glycoprotein and lysozyme were significantly increased predominantly in the ocular type, whereas the component of complement factor B was significantly increased especially in the neurological type of Behçet's disease. It is suggested that the changes in the concentrations of some plasma proteins may help our understanding of tissue involvement in Behçet's disease, as well as in the selection of therapeutic agents in this disease (Lehner and Adinolfi 1980). In patients with active disease, serum ferritin levels were increased and did not reflect serum iron levels, which could be especially helpful as there is no disease activity index for this disease (Odabas, Karakuzu et al. 2002), (Gonul, Gul et al. 2010). Patients with Behçet's disease had significantly lower median serum mannose-binding lectin levels compared to controls and more severe disease was more often in low mannose-binding lectin group (Inanc, Mumcu et al. 2005).

8. Conclusion and future views

Only examples of rheumatic inflammatory diseases (most of them with autoimmune background) were described and selected based on their prevalence and descriptions of APPs, which play crucial roles in enabling the protection and ultimately, the survival of the patient. There is a redundancy (known in biological systems) among APPs, with molecules having similar synthesis/production curves and providing similar functions, (such as CRP and SAA, or even more so, many moderate and minor APPs). This redundancy enables survival following infections, injuries and inflammation. However, the lack of a CRP high response found in the majority of cases of SLE and pSS implies its importance in homeostasis. SAA has not been measured as extensively as CRP in the past, however a pattern of its protein absence in the described diseases has not emerged in our study, leading to a speculation that SAA could be crucial in host protection and wound healing. Based on this, it is our recommendation that SAA be measured routinely, alongside with CRP, especially in diseases with inflammatory components, but negative or low CRP values.



In parallel, the balance/imbalance between pro- and anti-inflammatory, inhibitory and stimulatory, protective and degradative molecules, as well as antibody and antigen regulation, tilts/shifts the organism towards either a physiological, homeostatic condition or a pathological one. It seems that CRP and SAA are not only “major” (or highly abundant) in their concentrations in the APR, but also in their functions. And the moderate, minor and negative APPs play crucial supporting roles in allowing/enabling the modulation of the APR, alongside with their other roles (Arvidsson, Gudbjornsson et al. 1998).

Categorizing APPs in groups (ranging from major to minor) can be at times misleading, due to the fact that they can (in the majority of diseases) appear, for instance, as minor APP, however in rare diseases can be greatly elevated, such as ferritin in adult Still disease.

In general, earlier diagnoses require the detection of multiple markers, which can also differ based on disease staging, organ involvement or even patient development stages (ranging from neonatal, new-born, juvenile, adult and elderly). So, designing a more optimal approach/protocol for the clinician’s critical decision making process is a constant requirement. More studies targeting earlier disease development with a greater number of patients are necessary, along with a more personalized view of a patient’s physiology, especially to be able to compare diseased states with homeostatic ones.

In conclusion, APPs are not only disease markers, but also active players in physiology and pathology and can additionally represent one of the multiple hits that influence disease exacerbation, activity and outcome. Understanding mechanisms that modify the APR is an important step in developing new strategies for early detection, prevention and treatment of debilitating autoimmune diseases.

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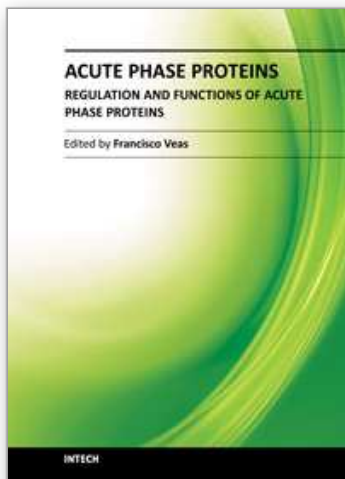
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