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## Acute Phase Proteins in Transplant Patients – Review

This review is to evaluate the usefulness of acute phase proteins in monitoring transplant patients.

Acute phase reaction is a non-specific immune response evoked by many different stimuli. Acute phase proteins (APPs) that play an important role in this reaction help to restore homeostasis. APPs concentration and glycosylation changes during acute and chronic inflammation are commonly known and they became a useful diagnostic tool to distinguish these two stages. They are very sensitive markers of inflammation though the reaction is not specific.

The main problem in transplantology is to distinguish between the graft rejection and bacterial or viral inflammation. The best and non-invasive markers of rejection in contrast to bacterial inflammation that in many cases accompanies transplantation are still being searched. APPs that may be regarded as markers of alteration in the cytokine network allow to control the survival of transplants under the immunosuppressive therapy. They are also useful markers of early acute and chronic rejection and also of different posttransplant complications.

The changes of APPs in serum of transplant patients are not organ specific, but their specificity becomes much better when correlated with other biochemical markers.

### Key words:

acute phase protein, acute phase response, transplantation, inflammation, C-reactive protein

### *Akute Phase Proteine bei Transplantierten – Welche Aussagewerte bieten Akute Phase-Proteine (APP) beim Monitoring transplantiertter Patienten?*

*Die Akute Phase-Reaktion (APR) ist eine unspezifische Immunantwort, ausgelöst durch unterschiedliche Stimuli. Akute Phase-Proteine (APP) tragen in diesem Kontext dazu bei, die Homöostase wiederzugewinnen. Änderungen der APP-Konzentration und der Glykosilierung sind als diagnostische Unterscheidungsmerkmale zwischen akuter und chronischer Entzündung bekannt; die Sensitivität der Marker ist sehr hoch, die Spezifität der Reaktion jedoch gering.*

*Ein entscheidendes Problem der Transplantationsmedizin liegt darin, zwischen einer Organabstoßung und einer bakteriellen oder viralen Entzündung zu unterscheiden. Die besten Marker einer Abstoßung – zur Abgrenzung gegenüber einer häufig gleichzeitigen bakteriellen Entzündung – sind gegenwärtig noch Gegenstand der Forschung. APP, als Marker von Änderungen im Zytokin-*

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*Network, lassen unter den Immunsuppression Rückschlüsse auf das Transplantat-Überleben zu: bei früher akuter und bei chronischer Abstoßung sowie anderen Komplikationen.*

*Die APP-Veränderungen im Serum transplantiertter Patienten sind nicht organspezifisch, doch eine Korrelation anderer biochemischer Marker lässt eine hohe Spezifität zu.*

**Schlüsselwörter:**

*Akute Phase Proteine, Akute Phase Reaktion, Transplantatabstoßung, Infektion, C-reaktive Proteine*

**Abbreviations**

A2M	$\alpha_2$ macroglobulin
ACT	$\alpha_1$ -antichymotrypsin
AGP	$\alpha_1$ -acid glycoprotein
Alb	albumin
APP	acute phase protein
APR	acute phase response
AT	antitrypsin
ConA	concanavalin A
CRP	C reactive protein
GVHD	graft versus host disease
IL	interleukin
INF	interferon
LBP	lipoprotein binding protein
MPO	mieloperoxidase
SAA	serum amyloid A
Tf	transferrin
TNF	tumor necrosis factor

**Introduction**

Trauma, bacterial or viral infection, hemorrhage or tissue injuries cause inflammatory response of the organism. It is unspecific and generalized and is accompanied by behavioral changes: fever, somnolence, anorexia, and by biochemical, hormonal and hemodynamic alterations: increased concentrations of cortisol and corticotropin, anemia, leukocytosis, trombocytosis, negative nitrogen balance, osteoporosis, cachexia, decreased gluconeogenesis [1]. This reaction comprises several features that allow organism to function in the inflammatory state, to defend itself against destructive effects of inflammation induced products, to induce faster reparatory processes and to restore homeostasis. All these mechanisms together are called acute phase response (APR) [2,3].

Cytokines released during APR by various cells, i.e. endothelial cells, monocytes and macrophages, T lym-

phocytes and fibroblasts, for example tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin 1- $\alpha$  (IL-1 $\alpha$ ), interleukin 1- $\beta$  (IL-1 $\beta$ ) and interleukin 6 (IL-6) [2-5] change, among others, expression of several genes for proteins produced in the liver. Some of them are intracellular hepatic proteins like transcriptional factors, metalothioneins, surface receptors; (they are commonly called acute phase regulated intracellular proteins – APRIP). Some of them are excreted by the liver cells to blood and called acute phase proteins (APPs): transport proteins, complement components, proteases inhibitors, antioxidants [5].

**Acute Phase Proteins**

Concentrations of some proteins change twice or several times, in case of C-reactive protein (CRP) or serum amyloid A (SAA) even 1000-fold. Proteins which concentration increases during APR are called positive APPs, whereas these which concentration decreases are negative APPs. The change in concentration may occur during the first day after trauma or during the next days after the stimulus. This was the basis for another classification of APPs: first line proteins' concentrations increase within hours reaching maximum on the second day and decreasing quickly, whereas second line proteins' concentrations start increasing on the second day,

reach maximum about one week after the stimulus and stay elevated for several days [1,3]; (Table 1).

Expression of genes for CRP, SAA and AGP alters under the influence of IL-1 $\beta$ , which may be enhanced by IL-6 [4,6], whereas expression of genes for fibrinogen, A<sub>2</sub>M and AT is induced by IL-6 and is enhanced by glukocorticosteroids [5].

IL-6 binds to IL-6 receptor causing dimerization of membrane proteins gp130 and activation of three Jak kinases (JAKs): JAK1, JAK2 and TYK2. Activated complex: IL6-IL6R-gp130-JAK causes phosphorylation of signal transducers and activators of transcription (STAT proteins): 1, 2 and 3. STATs form homo or heterodimers, and these are translocated to nucleus where they evoke transcription of several proteins, among others acute phase proteins [5,6].

**Functions of APPs**

APPs may play various roles during APR. CRP binds on a calcium-dependent manner various ligands, e.g. phosphorylcholine liberated from membranes of viruses, bacteria or own damaged cells, histones, lipoproteins HDL and LDL, it inhibits chemotaxis of neutrophils, production of nitrogen superoxide and platelets aggregation. SAA may also react with HDL and is much more sensitive marker of viral infection [3]. CRP and SAA bind immune complexes, cellular fragments or DNA, speeding up restauration of homeostasis and preventing from immunization with nucleic acids. Fibrinogen and complement components modulate repairing processes. Haptoglobin and ceruloplasmin act as antioxidants both in physiological and in pathological conditions and haptoglobin is additionally a stimulator of angiogenesis. AT and ACT are serine proteases' inhibitors, ACT may also bind DNA. AGP has several immunomodulatory functions, it

Tab. 1: Classification of exemplary APPs

Classification	Positive APP	Negative APP
First line	ACT, CRP, SAA	Alb
Second line	AGP, AT,	Tf

A<sub>2</sub>M -  $\alpha_2$ macroglobulin, ACT -  $\alpha_1$ -Antichymotrypsin, AGP -  $\alpha_1$ -acid glycoprotein, Alb-albumin, AT -  $\alpha_1$ -Antitrypsin, SAA - serum amyloid A, Tf- transferrin

inhibits lymphocyte migration to inflammatory sites, its role in Gram (-) bacterial infection was also reported [7,8]. Tf transports iron ions, whereas albumin is a transport protein for hormones, lipids and drugs. A2M may transport IL-6 in serum [9].

### Glycosylation of Acute Phase Proteins

In majority acute phase proteins are N-glycoproteins. In physiological conditions each protein appears in plasma in several variants, differing in content and kind of side oligosaccharide chains. All N-glycochains have a common core, consisting of three mannose molecules and two N-acetylglucosamine molecules. Additionally they contain various amount of sialic acid rests, bound via alpha 2-3 or alpha 2-6 link to galactose, one or more fucose molecules bound via alpha 1-3 to N-acetylglucosamine at the end of chain, via alpha 1-2 to galactose or via alpha 1-6 to pentasaccharide core. They differ also in degree of antennarity, where to the most basic biantennary structure a third or fourth antenna may be bound via alpha 1-3 and/or alpha 1-6 to mannose of the pentasaccharide core, producing tri- or tetra- or even more-antennary glycans. The feature of different oligosaccharide structure on the molecules of the same protein is referred to as major microheterogeneity. The number of variants of the same protein may reach even 20 and depends on the number of glycosylation sites on the protein chain: from two on transferin to five on AGP molecule [8].

During acute phase response a change in number of variants and in their proportion may occur, as well as new variants may appear, characteristic for either acute or chronic inflammatory conditions. Alterations in side oligosaccharide chains structures belong to posttranslational changes and are not limited to inflammatory reactions, but occur also in various physiological or pathological conditions, like pregnancy, stress or liver failure in alcoholics [2,10]. To estimate the degree of branching of the oligosaccharides a method called crossed affinity immunoelectrophoresis with Concanavalin A as a ligand is used. ConA binds biantennary and do not bind tri-, tetra nor

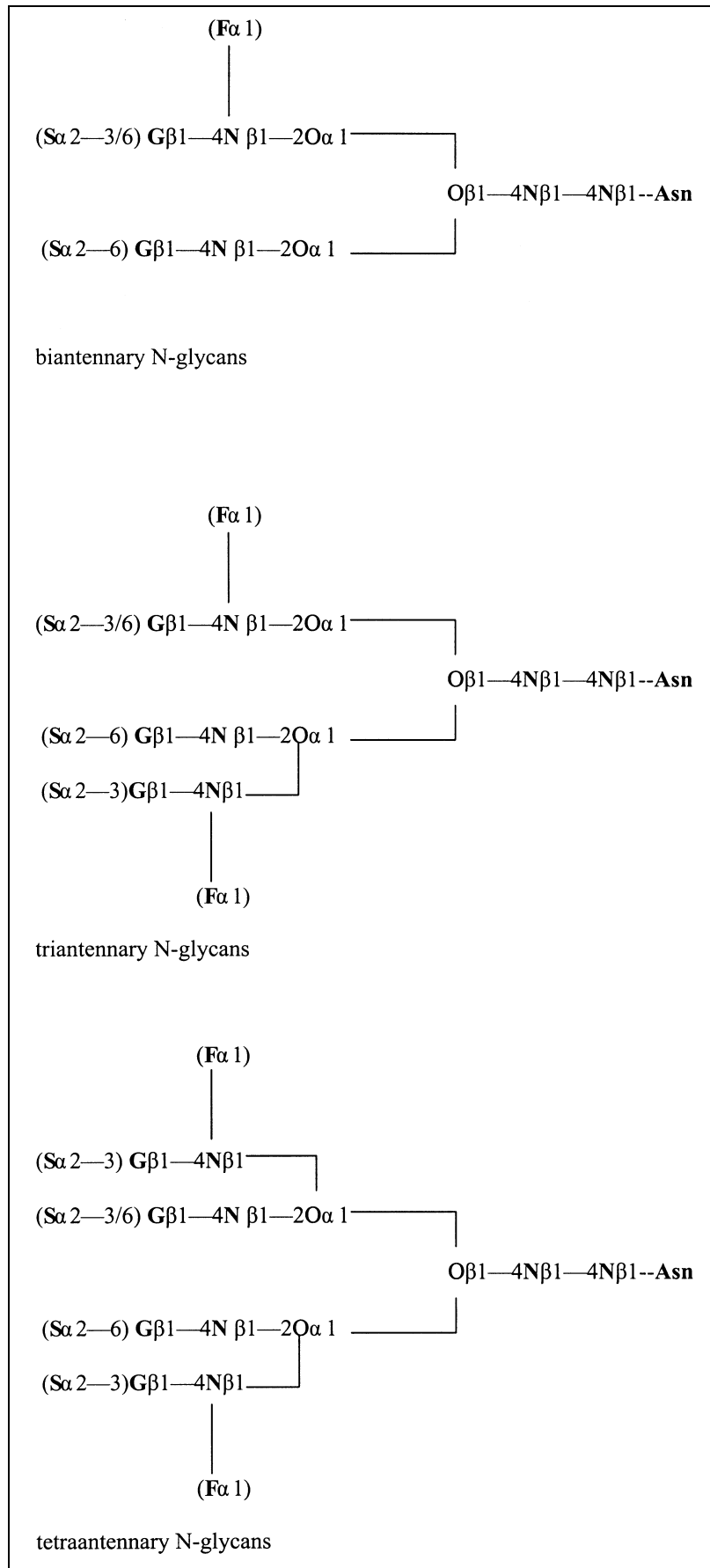


Fig. 1: General schema of bi-, tri- and tetraantennary N-glycans. [Asn]-asparagine, [S] sialic (neuraminic) acid, [G] galactose, [N] N-acetylglucosamine, [O]mannose, [F] fucose

more branched glycans, nor structures with bisecting GlcNAc. Therefore molecules of a protein divide into ConA-reactive variants (with predominantly biantennary glycans) and ConA non-reactive variants (more branched). Alterations in glycosylation of acute phase proteins are caused by cytokines, mainly IL-1, IL-6 and TNF alpha, and glucocorticoids [8]; it is worth to mention that alterations in glycosylation profile of a protein in plasma may occur faster than in its general concentration, what could suggest peripheral binding of selected variants or further processing in peripheral blood or tissues. Synthesis and glycosylation are regulated distinctly [8,11].

### **Diagnostic Significance of Determination of Acute Phase Proteins**

The possibility of determining clearly chronic or clearly acute character of glycosylation changes was found useful in diagnostic procedures [12-17]. Total concentration of acute phase proteins decreases slightly in chronic inflammatory conditions and is usually stable on the low level, whereas the concentrations of positive APPs increase markedly in acute conditions. Further characteristic features of acute inflammation are the lower degree of branching of side oligosaccharides, their shortening and desialylation or decreasing degree of fucosylation. For chronic inflammatory conditions both increase in branching and increase in fucosylation was described.

Analysis of acute phase proteins concentrations was also carried out in transplant patients, but the microheterogeneity was rarely analyzed in parallel.

Monitoring of alterations in both concentrations and glycosylation profiles of APPS and correlating of these changes with some other biochemical parameters may be an easy, fast and non-invasive method of recognizing the acute or chronic reaction of transplant rejection.

### **APPs in Heart Transplants**

There was a search for methods allowing to distinguish between inflamma-

tory reactions and transplant rejection. Markers of APR were correlated with other parameters. In transplant patients increases of VCAM-1, ICAM-1 and E-selectin were noticed, but it was not sure whether they resulted from inflammation or activation of the immune system (i.e. rejection reaction). Analysis of regression did not allow to distinguish the two reasons. Sensitivity and specificity of these measurements might be increased by correlating them with CRP, AT, C3 and C4 complement components and beta2-microglobulin [18].

An increase in CRP and other APPs concentrations is a marker of inflammation. In cases of bacterial infection their concentration decreases quickly, whereas in cases of transplant rejection their concentration stays increased for a long time and is accompanied by an increase in adhesion molecules' concentrations.

IL-6 stimulates the synthesis of angiotensinogen (renine substrate, RS), which is an APP and potential precursor of angiotensin II. Heart transplant causes acute phase reaction with an increase in IL-6 concentration followed by an increase in RS. This is a probable reason of the increase of angiotensin II followed by alterations in blood vessels of heart transplant patients [19].

### **APPs in Renal Transplants**

In early monitoring of the acute rejection of renal transplants the measurements of SAA and CRP is a very good method. In patients who obtained immunosuppressive drugs (cyclosporin, azathioprin and prednisolon) SAA level increased except those in whom rejection was absent. In some patients SAA increased faster than creatinine what could be used to introduce immediately anti-rejection treatment. In patients who rejected the transplant the CRP concentration was less changed than SAA. Parallel SAA and CRP increase may be regarded as marker of infection. SAA is a sensitive though not specific marker of acute rejection. CRP concentration remains low during rejection reaction, but increase during infection, what may be used to distinguish these two pathologies [16].

Everyday measurement of CRP concentration in monitoring of renal trans-

plant patients was proved to be a more sensitive marker of acute or chronic rejection, and bacterial or viral infection than measurement of WBC (white blood cells) and fever. It cannot be used, unfortunately, in steroid-resistant cases of rejection. It is another proof of its unspecificity despite of its high sensitivity [20].

Measurement of CRP and A2M in urine allows a non-invasive diagnostics of acute failure of the transplanted kidneys. Calculating the ratio between serum and urine CRP concentration may help the differentiation between urinary tract infection and renal graft rejection. At the same time the presence of granulocytes in urine may be detected by measuring mieloperoxidase (MPO) concentration. Parallel measurements of those three parameters (CRP, A2M and MPO) help to distinguish between transplant rejection and inflammation [21].

Monitoring of APR may also be useful in diagnosing of the risk of arteriosclerosis and alterations of the intima media in the course of chronic rejection [22]. In patients with chronic rejection higher concentrations of AGP, fibrinogen and soluble P-selectin were found, while no elevation of other adhesion molecules' concentration was noticed [23].

It seems that alterations in APPs are not organ-specific, but they are sensitive, especially when correlated with other markers like MPO or beta2-microglobulin.

To differentiate between rejection and infections also LPS-binding protein (LBP) is used. Its concentration increases in generalized Gram(-) infections, also a correlation was found between Gram(+) bacteremia and LBP concentration in transplant patients. In renal transplant patients increased LBP was found only during non-viral infections with acute lymphopenia [24].

### **APPs in Liver Transplants**

In serum of patients after liver transplants an increase in AGP, ACT, AT, Hp and A2M was described, correlating with rejection. Alterations in AGP and ACT were statistically significant. The serum level of beta2-microglobulin was increased in post-operative period and increased further only in cases of acute

rejection. The decrease of prealbumin concentration two-three days after rejection has been recorded.

Changes in APPs concentration in acute rejection of liver transplants seem similar to those described in inflammation or tissue damage, also in kinetics [9]. As the liver is directly responsible for APPs synthesis, the measurements of some APPs, namely AGP concentration and ACT concentration with glycosylation profile may be used for assessment of liver transplant. In contrast to kidney transplant CRP or SAA seem to play only a minor role.

In case of liver transplant rejection the concentration of ACT is markedly increased (up to 2300 mg/L). Variants with branched oligosaccharides dominate and the ratio of ConA non-reactive to ConA reactive variants, initially low, increases after the first week. It decreases after three weeks in all patients in whom there was no rejection. Increase of branched oligosaccharides within three weeks shows the chronic character of the inflammatory process, in contrast to acute reaction with mainly biantennary glycans just after the surgery.

Usually transaminases are used as markers of liver failure or insufficiency. However in case of graft acceptance transaminases activity did not decrease. On the other hand, in case of any damage of hepatocytes changes of activity of transferases responsible for acute phase proteins glycosylation occur. Therefore though it is not easy to estimate changes in APPs after liver transplant, measuring of ACT and estimation of its glycosylation profile may be a good marker of organ rejection. In patients with no rejection the normalization of ACT glycosylation profile within a few days after surgery was a good prognostic marker [25].

### APPs in Bone Marrow Transplants

The major cause of mortality and morbidity of patients after allogenic bone marrow transplantation (BMT) is bacterial infection, especially Gram-negative one, as they suffer from severe neutropenia [26].

Evaluation of CRP up-levels in serum of this patients helps identify the major transplant complications (MTC): hepatic veno-occlusive disease, pneumo-

cystis, severe endothelial leakage syndrome and graft versus host disease (GVHD) [27].

CRP levels change rapidly (>50 mg/l) in 0-5 days in serum of patients at risk of MTC and transplant-related mortality (TRM), also in children after BMT [28]. That is why this blood parameter is useful in selecting patients for preceding antiinflammatory treatment [27]. Concentration of CRP, an unspecific marker of tissue damage, is elevated both in infection and in GVHD [29]. In acute cases of this disease a good correlation was observed between patients status and TNF concentration, though this may not be true in particular cases. In contrast, elevated concentrations of CRP were observed in majority of cases, though it is not precise why it accompanies GVHD.

### Conclusions

APPs measurements may be of value in diagnosing transplant rejection. Elevated CRP concentrations were observed in majority of cases of kidneys or heart transplants and in GVHD.

Though these changes are not organ specific, they allow distinguishing between various posttransplant complications, like inflammation or arteriosclerosis. In studies on organ transplants the major problem is the early diagnosis of organ rejection versus viral or bacterial infection, often occurring in transplant patients, especially treated with strong immunosuppressive drugs. The functioning of the immune system should be monitored during immunosuppressive therapy. Too long an immunosuppression may cause that early signs of transplant rejection will be overlooked [22]. Biopsy still remains the most reliable, though invasive method. At the same time monitoring of APR with the use of measurements of APPs concentrations and glycosylation profiles may serve as marker of the cytokine network functioning, thus – of the balance in the immune system and various inflammatory processes. As an example the monitoring of patients suffering from pancreas cancer may be shown, as APR may predict the alterations in the cytokine network that may in those patients lead to cachexia [15].

Tab. 2: Markers of infection, posttransplant complications, rejection reaction in patients after heart, bone marrow, kidney and liver transplantation (↑-increase, ↑↑-greater increase, ↓decrease)

Organ	Markers of infection	Markers of graft rejection	Markers of transplant-related complications
Heart	↑CRP, ↑AT, ↑C3, ↑C4, ↑beta2-microglobulin concentration decrease quickly	↑CRP, ↑AT, ↑C3, ↑C4, ↑VCAM-1, ↑ICAM-1, ↑E-selectin concentration increased for a long time	↑RS
Kidney	↑SAA, ↑↑CRP, ↑LBP in urine: ↑A2M, ↑CRP, ↑MPO,	↑SAA, ↑CRP	↑AGP, ↑fibrinogen, ↑P-selectin (arteriosclerosis)
Bone marrow	↑CRP (>50 mg/l)	↑CRP (>50 mg/l for 5-10 days after BMT; >100 mg/l to 100 days after BMT)	↑CRP (>50 mg/l)
Liver		↑AGP, ↑ACT, beta2-microglobulin, ↑branched glycoforms of ACT, ↓prealbumin	

Many cytokines are responsible for the induction of the rejection reaction: IL-2, IL-7, IL-12, IL-15, IFN-gamma, TNF-alpha, IL-6 [22]. At the beginning of the inflammatory process the cytokines are produced that lead to APR, namely TNF-alpha and IL-6. Measurements of APPs may even be more reliable than the concentration of IL-6, as this cytokine is produced locally and quickly catabolized, what makes its measurements difficult. The level of IL-6 increases within two hours and reaches maximum after 12 hours. The concentration of CRP increases slower, though it is a first line APP: it increases after eight hours and reaches maximum in 48-72 hours [2]. The measurement of APPs concentrations may be a better marker of cytokines production than measuring directly cytokines. Monitoring of APPs is a non-invasive method: serum samples after routine laboratory tests may be used, thus creating no extra ballast for the patient. Proper diagnostics of the course and intensity of inflammatory processes via monitoring of APPs concentrations and microheterogeneity may improve the treatment of the transplant patients resulting in transplant survival.

## Acknowledgement

I thank Magdalena Sobieska for advice and support during writing this review and technical assistance in English translation.

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