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Review Article

Dentistry Section

Acute Phase Proteins and Their Role in Periodontitis: A Review

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ABSTRACT

Acute phase proteins are a class of proteins whose plasma concentration increase (positive acute phase proteins) or decrease (negative acute phase proteins) in response to inflammation. This response is called as the acute phase reaction, also called as acute phase response, which occurs approximately 90 minutes after the onset of a systemic inflammatory reaction. In Periodontitis endotoxins released from gram negative organisms present in the sub gingival plaque samples interact with Toll- like receptors (TLR) that are expressed on the surface of Polymorphonuclear leucocytes (PMNs) and monocytes which are in abundance in periodontal inflammation. The complex formed due to interaction of Endotoxins and TLR activates the Signal transduction pathway in both innate and adaptive immunity resulting in production of Cytokines that co- ordinate the local and systemic inflammatory response. The pro inflammatory cytokines originating at the diseased site activates the liver cells to produce acute phase proteins as a part of non specific response.

The production of Acute phase proteins is regulated to a great extent by Cytokines such as IL-1, IL-6, IL-8, TNF-α and to a lesser extent by Glucocorticoid hormones. These proteins bind to bacteria leading to activation of complement proteins that destroys pathogenic organisms. Studies have shown that levels of acute phase proteins are increased in otherwise healthy adults with poor periodontal status. This article highlights about the synthesis, structure, types and function of acute phase proteins and the associated relation of acute phase proteins in Periodontitis.

Keywords: Acute phase proteins, Cytokines, Inflammation

INTRODUCTION

Acute-phase proteins (APP) are defined as proteins whose serum concentration is altered at least 25% in response to inflammation and includes proteins of the complement, coagulation and fibrinolytic system, antiproteases, transport proteins, inflammatory mediators and others [1,2]. APP are the sensitive markers for evaluating the status of inflammation. Increased levels of APP are associated with increased risk for cardiovascular events in both health and Coronary heart disease patients and have been suggested to associate with infectious disease such as Periodontitis [3,4].

CLASSIFICATION

App acute phase proteins: are divided into two groups: Type I and Type II. Type I Serum amyloid A, C-reactive protein, α1-acid glycoprotein, Complement C3 induced by the proinflammatory cytokines (IL-1 and tumour necrosis factor). Type II acute App: Fibrinogen, Haptoglobin, α2-macroglobulin, α1-antichymotrypsin, α1-antitrypsin induced by the IL-6 like cytokines [5].

They are classified as–

1. Positive acute phase proteins
2. Negative acute phase proteins

Positive APP are those which increases with inflammatory response and the Negative APP are those which shows a decrease in serum concentration with increase in inflammation [6].

Positive acute phase proteins includes C-reactive protein, Serum amyloid A, Serum amyloid P component, Complement factors, Mannan-binding lectin, Fibrinogen, prothrombin, factor VIII, Von Willebrand factor, Plasminogen, Alpha 2-macroglobulin, Ferritin, Ceruloplasmin, Haptoglobin, Alpha 1-antitrypsin and α1-antichymotrypsin. Their function includes Opsonisation of microbes, Recruitment of immune cells to inflammatory site, Induces enzymes which degrade the extra cellular matrix. Chaemotaxis, lysis and clumping of target cells. Complement activation, Degradation of blood clots, Inhibits coagulation and fibrinolysis by inhibiting thrombin. Binds haemoglobin and inhibits microbe iron uptake. Serpin down regulates inflammation [5].

Negative acute phase proteins include Antithrombin, Albumin, Transferrin, Transthyretin, Transcortin, and Retinol – binding protein. Their function includes increased coagulation, Increase free cortisol in blood, restoring homeostasis after stress [5].

Based on the response to inflammatory stimulus they are classified as

1. Strong acute phase proteins
2. Moderate acute phase proteins
3. Weak acute phase proteins

Strong acute phase proteins include C- reactive proteins, α2-macroglobulin, serum amyloid A which responds rapidly to inflammatory stimuli and their serum levels may increase several hundred folds. Moderate acute phase proteins include Haptoglobulin, Fibrinogen, α1- antitrypsin which can increase 2-10 folds. Component C3 and ceruloplasmin are considered weak acute phase proteins that may increase upto 2 folds [5].

REGULATION OF APP PRODUCTION

Cytokines are involved in triggering the acute phase response. Van Miert distinguished three main groups of cytokines that regulate the production of APP.

1. Cytokines which act as positive or negative growth factors include IL-2, IL-3, IL-4, IL-7, IL-10, IL-11, IL-12, granulocyte-macrophage colony stimulating factor.
2. Cytokines having pro-inflammatory properties are TNF-α/β, IL-1α/β, IL-6, IFN-α/γ, IL-8, macrophage inhibitory protein-1.
3. Factors with anti-inflammatory activity – IL-1 receptor antagonists, soluble IL-1 receptors, IL-1 binding protein, TNF-α binding protein [7].

IL-1 is considered an important mediator of inflammation because of its presence at the inflammatory sites and its ability to induce inflammatory response. Induction of IL-6 by IL-1 partly explains its role in App production. IL-1 increases the transcription of some App and decrease the transcription of other hepatic proteins [6].

IL-6 is a pleiotropic cytokine involved in the regulation of acute-phase response, immune response and haematopoiesis. In several inflammatory conditions and during an acute-phase response induced by the administration of endotoxins or septic shock, increased leukaemia inhibitory factors levels in plasma and inflammatory body fluids results in induction of type II App [4].

Tumour necrosis factor is considered a major inflammatory mediator. The effects of tumour necrosis factor on acute-phase induction include increased biosynthesis of complement proteins factor B and C3 and α1 anti-chymotrypsin. Tumour necrosis factor also decreases the biosynthesis of albumin and transferrin. All three cytokines (IL-1, IL-6 and tumour necrosis factor) can also be carried via the blood to distant sites, inducing an acute-phase reaction [5].

Glucocorticosteroids decrease the level of IL-1, tumour necrosis factor, and IL-6 in the peripheral blood via transcriptional and post transcriptional routes and prolong their impact on the target cells through the elevation of the expression of their receptors. Prostaglandins also inhibit the release of IL-1 from macrophages. There exist apparent feedback mechanisms involving both liver synthesized App and neuro endocrine factors from the central nervous system, which contribute to regulation of the acute-phase response to inflammation [6].

POSITIVE ACUTE PHASE PROTEINS

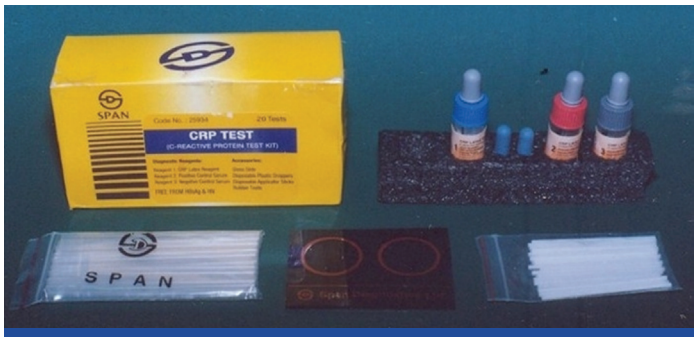
C-Reactive Protein

C-reactive protein (CRP) is an important App that was discovered in 1930. CRP is closely linked with IL-6 an important pro-inflammatory cytokine, which acts as the primary inducer of CRP synthesis by the liver. It has been shown that plasma level of CRP is mainly regulated at the transcriptional level induced by IL-1 [1].

CRP is primarily synthesized by hepatocytes, while extra hepatic synthesis of CRP has been reported in peripheral blood lymphocytes, alveolar macrophages, brain neurons, respiratory tract, atherosclerotic plaque, coronary artery, kidney, adipose tissue, lung epithelial cells. CRP shows association with smoking, obesity, coffee consumption, triglycerides, diabetes and periodontal disease. In the oral cavity, CRP has been detected in saliva and GCF, whereas it remains unknown whether gingival tissues is capable of producing CRP. It is hypothesized that human gingiva is capable of producing CRP along with IL-1 [4]. When bound to bacteria it promotes the binding of complement further facilitating phagocyte uptake. This process of coating protein enhances the phagocytosis similar to opsonization by the antibodies [5].

C-reactive protein is normally present in ng/ml quantities but may increase dramatically to hundreds of mg/ml within 72 hours following injury of the tissue. This represents a 100- to 1000-fold increase within hours of tissue damage. Elevated levels of C-reactive protein (CRP) and decrease plasma adiponectin are associated with increased risk of atherosclerosis [6]. There is evidence that Periodontitis and coronary artery disease (CAD) are linked together by inflammatory stimuli such as heat, trauma, infection and hypoxia [8]. Inflammatory mediators, IL-1 IL-6 and TNF-α are released in periodontitis and stimulate hepatocytes to produce CRP. In this manner, it can be expected that, in the presence of chronic periodontitis, higher serum CRP levels would be found [9]. After acute tissue damage, CRP levels rise in serum or plasma within 24 to 48 hours and reach a peak during the acute stage (as high as thousand fold). Their levels decrease with the resolution of inflammation or trauma. Thus CRP levels provide information for diagnosis, monitoring and therapy of the inflammatory process and its associated disease [8].

CRP are measured by immunoelectrophoretic, immunoturbidimetric assays, latex slide agglutination method, ELISA or an immunofluorescent assay. A rapid chair-side diagnostic test is used to detect CRP levels which help in assessing the periodontal disease activity [Table/Fig-1] [10].



[Table/Fig-1]: C-Reactive Protein Test Kit

Recent studies by Slade et al., demonstrated a correlation between Periodontitis and elevated C- reactive protein levels and evaluated association among periodontal disease and established risk factors for elevated CRP [11].

Fitzsimmons TR conducted a study to determine the independent and C-reactive protein (CRP) in the gingival crevicular fluid of periodontitis and demonstrated a correlation between Periodontitis and elevated C- reactive protein levels [12].

Megson E et al., demonstrated a correlation that Periodontitis is associated with elevated C-reactive protein (CRP) in both serum and gingival crevicular fluid (GCF) [13].

Anne C et al., investigated the effects of nonsurgical periodontal therapy on levels of high-sensitivity C-reactive protein in the sera and its association with body mass index and high density lipoprotein in subjects with severe periodontitis and found periodontal therapy decreased the levels of circulating high-sensitivity C-reactive protein [14].

Serum Amyloid–A

Serum amyloid A is a precursor of protein amyloid A in secondary amyloidosis deposited in interstitium of tissues and interfere with normal tissue function. Serum amyloid A comprises multiple isoform designated SAA1, SAA2 and SAA4. The isoforms of serum amyloid A, A-SAA1 and A-SAA2, are upregulated by inflammatory cytokines by as much as 1000-fold during inflammation like C-reactive protein and monitored as a surrogate marker of inflammation [1].

Graziani F et al., conducted a study to determine whether non-surgical periodontal treatment in subjects with generalized chronic periodontitis (GCP) add some beneficial effect on renal function. Greater increase of C-reactive protein (CRP) and Serum Amyloid A (SAA) was observed in the first 24 hours and decreased after 30 days of treatment. Periodontal infection with intensive therapy may increase endothelial function and may reduce systemic inflammatory markers acting on the risk of serious diseases [15]. The kinetics of serum inflammatory markers are observed after a course of treatment comprising surgical and non-surgical treatment of chronic periodontitis (CP) and found marked increase in serum levels of CRP and SAA in 24 hour after non-surgical therapy and periodontal surgeries [16].

Tetsuo Kobayashi et al., assessed the effect of a fully humanized anti-TNF-α monoclonal antibody, adalimumab (ADA), on the periodontal condition of patients with Rheumatoid Arthritis (RA) and to compare serum protein profiles before and after ADA therapy. Complement factor H, serum amyloid A, complement component 4, phospholipase D and α-1-acid glycoprotein were assessed and these serum proteins decreased after ADA treatment [17].

Plasminogen

The plasminogen-activating system is of prime importance in extracellular proteolysis. It acts in physiological and pathological reactions, neoplastic growth and its invasion [15]. Plasminogen activators are serine proteases.

They are of two types:

1. Tissue/blood vessel type PA (t-PA)
2. Urokinase type PA (u-PA).

The t-PA and u-PA form part of the complex enzyme cascade which is involved in fibrinolysis for conversion of proenzyme plasminogen into the broad-spectrum proteinase and plasmin. In periodontitis plasmin is formed at sites of inflammation, activates the proMMPs into proteases which are specific for elastin and collagen, also responsible for the degradation of fibrin and extracellular matrix (ECM) [18].

Studies have indicated higher concentrations of t-PA and PAI-2 in GCF suggests that they are involved in the aggravation of gingival inflammation. Furthermore, Xiao et al., have stated that t-PA and PAI-2 play a significant role in periodontal tissue destruction and tissue remodeling and used as clinical markers in GCF to evaluate the periodontal disease and treatment [19]. In a recent study, it is found that elevated GCF levels of t-PA and PAI-2 in cyclosporine A induced gingival overgrowth patients suggests involvement of PA system in the pathogenesis of side effect of Cyclosporine A therapy [20].

Fibrinogen

Fibrinogen is one of the App synthesized mainly by hepatocytes whose levels are elevated during infections and inflammatory conditions including periodontal disease. It is a 340 kDa glycoprotein made up of 2 identical sub units joined together by disulphide bonds. It functions as a blood coagulation factor in primary homeostasis in support of platelet aggregation and in secondary homeostasis in fibrin clot formation at the site of vessel injury [21].

Fibrinogen levels can be elevated 2 to 10 fold during inflammatory process. Fibrinogen is also produced by pulmonary and intestinal epithelial cells in response to infections and pro inflammatory cytokines and participates in localized acute phase responses during inflammatory process. Fibrinogen production is also stimulated by degradation products of fibrinogen or fibrin and indicates a feedback amplification loop that requires macrophages.

Studies suggest that excessive fibrinogen production might play a role in up regulating host immune response. In addition there is a relationship between the 455G/A polymorphism in the 5'frankling region of the β-fibrinogen gene promoter and increased fibrinogen levels representing risk for chronic periodontitis [21].

Graziani F assessed serum fibrinogen levels in subjects with generalized chronic periodontitis (GCP) with renal disease. Fibrinogen showed mild increase in the first 24 hours of non-surgical periodontal therapy and normalized after 30 days [15].

Mannan – Binding Lectin

Mannan – binding lectin (MBL) is an important molecule of innate immunity. It stimulates the classical complement pathway as an opsonin. It also acts as a weak App. It plays a role in the defense against invading micro organisms in periodontitis. MBL is produced in the liver and it belongs to the family of collectins. Collectins contain a collagen – like region and a carbohydrate binding lectin domain. In this way MBL can recognize carbohydrate structures, specifically the terminal mannose groups on the surface of a variety of microorganisms. These include Neisseria *meningitides*, Candida species, *Aspergillus fumigates*, *Staphylococcus aureus*, β-haemolytic group A streptococci and anaerobic bacteria like *Bifidobacterium bifidum* and *Veillonella dispar* [22].

Interestingly the periodontal pathogens *A.actinomycetemcomitans* and *P.gingivalis* also appear to have mannan rich polysaccharide. When ligated to periodontal bacteria, MBL interacts with serum derived serine proteases known as MBL-associated serine proteinases (MASPs) and forms MBL complex. MBL complex and the carbohydrate patterns on the bacteria interacts with C4 and activates the classical complement pathway in an antibody independent manner. MBL are on an average 1.2 to 1.6 μg/ml. Subjects with levels below 0.5 to 1.0μg/ml are considered MBL deficient. MBL plasma levels have been reported to increase during infections and inflammatory processes [23].

Maffei G et al., investigated whether MBL levels are increased in periodontitis, and whether individual's deficient for MBL are more susceptible to periodontitis. MBL plasma concentrations were not significantly different in moderate and severe periodontitis compared to controls and MBL deficiency was not related to susceptibility for periodontitis [23].

Louropoulou A et al., investigated the correlation of six functional polymorphisms in the MBL gene with MBL plasma levels in relation to periodontitis and found that high producing genotypes had significantly higher MBL plasma levels than low-producers and deficient subjects [24].

Haptoglobin

Haptoglobin (Hp) is a positive App, strongly binds haemoglobin, has anti-inflammatory capabilities and binds to CD11b/CD18 integrins representing major receptors on the cell membranes of leukocytes. Its quantity may decrease in massive erythrolysis and when blood is haemolytic. Determination by haemoglobin binding assays may give unreliable results. Haptoglobin binds and removes free haemoglobin released by intravascular haemolysis by forming a complex that is rapidly cleared by hepatocytes [1]. Following injury, infection or inflammation haptoglobin increases 2 to10 folds [5].

Haigh BJ et al., investigated changes in the salivary proteome associated with active periodontitis, identified haptoglobin as host defence component that have not been linked previously to this disease and suggested haptoglobin a new potential biomarker for monitoring disease activity in periodontitis [25].

Giannopoulou et al., compared the effect of Photodynamic Therapy, Diode Laser, and Deep Scaling on Cytokine and App Levels in GCF of Residual Periodontal Pockets. No significant differences were observed among the three treatment modalities at any time point for haptoglobin [26].

CD14

CD14 is an App expressed on the surface of various cells such as monocytes, macrophages, neutrophils, chondrocytes, B cells, dendritic cells, gingival fibroblasts, keratinocytes, and human intestinal epithelial cell lines. CD14 was initially described as a specific receptor for LPS of Gram-negative bacteria, receptor for peptidoglycan of Gram-positive bacteria and present to monocytes. CD14 level in the serum of normal adult human represents a 1000-fold excess of the LPS level seen in fatal septic shock patients. Several clinical studies reported serum levels of CD14 elevated in inflammatory conditions, such as Kawasaki disease, atopic dermatitis, liver disease, rheumatoid arthritis (RA), systemic lupus erythaematosus, primary Sjogren's syndrome and Periodontitis. Recently, sCD14 is demonstrated as a regulatory factor capable of modulating cellular and humoral immune responses by interacting directly with T and B cells [27].

The levels of sCD14 were elevated in the different inflammatory conditions and correlated with those of CRP and IL-6. The role of inflammation and IL-6 on CD14 expression in the liver was finally confirmed in an experimental model of acute-phase response mice

injected with turpentine. These data provide first information about the role of IL-6 on the regulation of CD14 expression in liver cells and show that CD14 behaves like a type 2 APP invivo [27].

Lactoferrin

Lactoferrin (Lf) is an iron-binding glycoprotein in saliva that is produced by neutrophils and glandular epithelial cells. The molecule possesses bacteriostatic, bactericidal, anti-inflammatory, fungicidal and antiviral properties. It is an important component of innate immunity, specifically in the context of protecting mucosal surfaces from microbial infections. Lf plays an essential role in iron delivery and in the regulation of iron homeostasis. It can be found in two forms: the iron free 'Apo-Lf' form; or the iron bound 'Fe-Lf' form. It is well established that Lf inhibits bacterial adhesion by iron sequestration [28].

Lactoferrin is produced in a number of tissues and is frequently found in human exocrine secretions such as tears, saliva, sweat, colostrum and milk. Polymorphonuclear leucocytes store large amounts of lactoferrin in their secretory granules.

Glimvall P et al., investigated differences in concentrations of salivary lactoferrin in subjects with and without periodontal disease. Subjects with chronic periodontits showed higher concentrations of lactoferrin in stimulated whole saliva compared with periodontally healthy control subjects [29].

Pentraxin-3

Pentraxin–3(PTX3) is an App, synthesis is stimulated in macrophages, endothelial cells, myeloid cells, and dendritic cells by cytokines and endotoxins such as bacterial products, interleukin-1, and TNF [9–11]. It is expressed in response to a variety of inflammatory or infectious stimuli and interacts with different ligands. Interaction of PTX3 with surface immobilized Complement C1q results in activation of classical complement cascade. It is a true independent indicator of disease activity [30].

Pradeep AR et al., compared the levels of Pentraxin-3 in GCF and Plasma in Periodontal Health and Disease. GCF and plasma PTX3 concentrations increased in subjects with periodontitis, considered a marker of inflammatory activity in periodontal disease [31].

Pınar G et al., evaluated saliva and serum levels of PTX3 in patients with generalized chronic and aggressive periodontitis and defined PTX3 as diagnostic tools for periodontal inflammation [32].

Ceruloplasmin

Ceruloplasmin is also an acute phase reactant seen to increase in inflammatory conditions, helps in transfer of copper in body and influences the uptake of iron into the cells because of its property of conversion of ferrous form of iron to the ferric form, due to which alterations in serum iron are often accompanied by changes in serum ceruloplasmin.

Recent studies reported that Serum ceruloplasmin levels increased in both aggressive and chronic periodontitis patients, but more levels in aggressive periodontitis patients and is a potential marker for diagnosis of periodontitis [33].

Ferritin

Ferritin is an acute-phase reactant, elevated in many chronic inflammation diseases. Its main function is to store iron in a soluble nontoxic form, protecting the cell from iron-mediated oxidation-reduction reactions. It acts as a delivery mechanism in circulation and levels in serum usually reflect total body iron stores.

Recent studies reported increased Serum ferritin levels in patients with chronic periodontitis and decrease to control levels post-treatment [34].

YKL-40

YKL-40 is a novel potential inflammatory marker in relation to both acute and chronic inflammation. It is a member of "mammalian chitinase-like proteins" but has no chitinase/enzymatic activity and secreted by activated neutrophils and macrophages in acute or chronic inflammation. YKL-40 is also shown to be produced by vascular smooth muscle and endothelial cells, arthritic chondrocytes, cancer cells and embryonic and fetal cells. It probably has a role in cell adhesion, migration, proliferation, and differentiation, inflammation, and protection from apoptosis. In addition, YKL-40 is a growth factor for connective tissue (CT) cells (fibroblasts, chondrocytes, and human synovial cells) and initiates a signaling cascade in these cells that leads to increased cell proliferation. Play a central role primarily in pathologic conditions associated with the homeostasis [35].

Recent studies reported increased secretion of YKL-40 is related to the pathogenesis of a variety of inflammatory diseases. Plasma and serum levels of YKL-40 are higher in patients with several systemic diseases. YKL-40 levels in GCF as well as serum YKL-40 and IL-6 levels increased from gingivitis to periodontitis [35].

NEGATIVE ACUTE PHASE PROTEINS

Albumin and Transferrin

Albumin and transferrin, the serum iron transport protein, are decreased during inflammation, potentially to starve the microorganisms of iron required for growth and virulence expression. Inflammation and malnutrition both reduce albumin concentration by decreasing its rate of synthesis [36].

It appears that cytokines IL-1, IL-6 and TNF-α are important down regulators of the synthesis of these acute-phase reactants. Recent studies reported that the number of untreated teeth was a significant factor associated with serum albumin concentration in elderly individuals. Iwasaki et al., indicated that there might be an inverse relationship between periodontal disease and serum albumin concentration [37].

Retinol- Binding Protein (RBP)

Vitamin A in plasma circulates as retinol. Retinol binding protein is the specific protein to which retinol (vitamin A alcohol) is bound in plasma. Retinol binding protein (RBP) is composed of 182 amino acid residues. RBP plays a key role in vision [38]. It also has an important role in maintenance of epithelial function. Newly synthesized retinol-binding protein (RBP) obtains one molecule of retinol in the endoplasmic reticulum of liver hepatocytes. This protein is then secreted into the plasma where it occurs in complex with thyroxine-binding pre albumin. Retinol plays a crucial role in the growth and differentiation of various body tissues [38].

Types of retinol binding protein

1. Plasma retinol binding protein- the retinol transport vehicle in serum.
2. CRBP I/II- cellular binding proteins involved in transport of retinol and metabolites into retinyl esters for storage or retinoic acid.
3. CRABPs- cellular retinoic acid binding proteins that are capable of binding retinol and retinoic acid with high affinity [38].

FUNCTIONS

In blood, RBP is bound to transthyretin and functions as a carrier protein for thyroid hormones, serves to prevent the loss of the smaller protein from the circulation by alteration in the renal glomeruli. The tertiary complex transthyretin, RBP, retinol thus serves to transport retinol in the circulation and to deliver it to target tissues. It has been established that retinol enters most of its target cells in the form of free retinol, unaccompanied by the binding protein [39,40].

CONCLUSION

The acute phase reaction can be used for assessment of general health, including starvation and growth. They are more useful for

monitoring periodontal health than the cytokines, because the latter are cleared from the circulation within a few hours, whereas acute phase protein levels after a single stimulus remain unchanged for 48 hour or longer. The acute phase reaction offers a biological effect mechanism appropriate to include in future systems for assessing periodontal health, its disease activity before and after treatment.

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