Review Article

Acute phase reactants - A review

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Abstract:

The acute phase refers to physiological and metabolic alterations that ensue immediately after onset of infection or tissue injury. A variety of changes in the organism act in concern to neutralize the inflammatory agent and faster healing of damaged tissues. In contrast with the specificity of cellular and humoral immunity, the acute phase changes are nonspecific and occur in response to many conditions.

Periodontal disease is a chronic inflammatory process that occurs in response to a predominantly Gram-negative bacterial infection originating from dental plaque. Increased levels of acute-phase proteins have been noted with gingival inflammation, including during experimental gingivitis and periodontitis, reflecting the locally stressed environment. Here, an attempt is made to discuss the importance of acute phase reactants.

Keywords: Acute phase reactants, periodontal disease.

Introduction:

The alterations which are brought about during inflammation are likely to be the acute-phase reaction which represents an early and highly complex reaction of the organism to a variety of injuries such as bacterial, viral or parasitic infection, mechanical or thermal trauma, ischemic necrosis, or malignant growth.

The purpose of these responses is to restore homeostasis and to remove the cause of its disturbance. Characteristic features of the systemic acute-phase response include (i) fever, (ii) neutrophilia, (iii) changes in lipid metabolism, (iv) hypoferremia, (v) increased gluconeogenesis, (vi) increased (muscle) protein catabolism and transfer of amino acids from muscle to liver, (vii) activation of the complement and coagulation pathways, (viii) hormonal changes, and (ix) induction of acute-phase proteins.[1] The tissue macrophage is the cell most commonly regarded as initiating the acute-phase response through direct stimulation and secretion of various cell communication factors.[2]

An additional acute phase response is an increase in the polymorphonuclear leukocyte and platelet count in the blood.

The acute phase response is a primary defense reaction and therefore protects against bacterial products such as endotoxin. Acute phase responses are thus elicited following infections, surgical wounds or other traumas such as burns and myocardial infarctions.

While the etiological role of bacteria has been firmly established in vitro and in vivo, the researchers have begun to identify local and systemic inflammatory processes that encourage a pathological response to an initial, commensal microflora.

Pro-inflammatory cytokines increase production of more cytokines, enhances Natural killer (NK) cytotoxicity, causes pro-inflammation by inducing cytokines and ICAM-1 and VCAM-1 on endothelium.

Pro-inflammatory cytokines and mediators are significantly elevated, with gingival inflammation during the destructive phase of periodontitis. The clinical findings in periodontitis have emphasized the local (periodontium) nature of the inflammation and tissue destruction within the oral cavity. One consequence of these localized gingival inflammatory reactions has been the identification of elevated levels of various acute phase proteins in the gingival crevicular fluid. These have included α2-macroglobulin, α2-antitrypsin and C-reactive protein, which are altered in the crevicular environment. Cytokines appear to play a major role in the clinical symptoms and tissue destruction associated with progressing periodontitis.

Since the acute-phase response plays a central role in promoting healing, periodontitis as a wound-healing problem would be directly affected.

The purpose of this paper is to discuss the importance of acute phase reactants.

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General review

The alterations which are brought about during inflammation are likely to be mediated through the release of various inflammatory mediators in the inflamed tissues, including reactive oxygen species, nitrous oxide and arachidonate metabolites (Table 1).[3]

Table 1: Metabolites of arachidonate metabolism in the acute-phase reaction.[5]

Mediator	Function
Thromboxane, A_2	Vasoconstriction
Prostaglandins I_2 ,E_2 D_2 and $F_{2\alpha}$	Vasodilation
Leukotriene B_4	Phagocyte chemotaxis
Leukotrienes C_4, D_4, and E_4	Smooth-muscle contraction

The synthesis of these acute-phase proteins has been shown to be regulated by cytokines and to a lesser extent by glucocorticoid hormones, cytokines related to the acute phase response can be divided into three groups; (Table 2).[4]

Table 2: Cytokines related to acute phase response.[4]

	Group	Function	Name
1.	Pro inflammatory cytokine	Initiate or enhance the cascade of events.	Tumour necrosis factor α, interleukin 1 (IL-1), interferon-γ and IL-8.
2.	Interleukin-6 type cytokine	Responsible for the main systemic features of acute phase response	IL-6, leukaemia inhibitory factor, IL-11, oncostatin M, ciliary neurotrophic factor and cardiotrophin-1.
3.	Anti inflammatory cytokines	Down regulates the acute phase responses	IL-10, IL-4, IL-13, transforming growth factor β

The majority of the acute--phase proteins are glycoproteins, which play a variety of roles in the homeostatic response to injury.

Acute phase response takes place by changes in a heterogenous group of proteins which consists of around 30 proteins (Table 3).[4]

Characteristics of the acute-phase reaction response molecules :

Acute -phase proteins serve important functions in restoring homeostasis after infection or inflammation. These include hemostatic functions (such as fibrinogen), microbicidal and phagocytic functions (such as complement components or C-reactive protein),

Table 3: Human Acute Phase Proteins.[4]

Increased proteins	
Complement System	C3,C4,C9 Factor B CI inhibitor C4b binding protein Mannose binding lectin
Coagulation and Fibrinolytic System	Fibrinogen Plasminogen Tissue plasminogen activator Urokinase Protein S Vitronectin Plasminogen Activator lnhibitor-1
Antiproteases	Alpha 1-Protease inhibitor Alphal-Antichymotripsin
Transport proteins	Seruloplasmin Haptoglobin Hemopexin
Inflammatory Responders	Phospholipase A2 Lipopolysaccharide binding protein lnterleukin-1 receptor antagonist Granulocyte colony stimulating factor
Others	CRP Serum amyloid protein A Alphal-asit glycoprotein Fibronectin Ferritin Angiotensinogen
Decreased proteins	Albumin Transferrin Transthyretin Alpha 2-HS glycoprotein Alpha -feto protein Thyroxin binding protein Insulin like growth factor 1 Factor 12

antithrombotic properties (such as α1 -acid glytoprotein) and antiproteolytic properties which are important to contain protease activity at sites of inflammation (such as α2 -macroglobulin, α1 -antitrypsin, α1- antichymotrypsin).[1]

Acute phase reactants in periodontitis:

Pro-inflammatory cytokines and mediators are significantly elevated, with gingival inflammation during the destructive phase of periodontitis.[4,5] The clinical findings in periodontitis have emphasized the local (periodontium) nature of the inflammation and tissue destruction within the oral cavity. One consequence of these localized gingival inflammatory reactions has been the identification of elevated levels of various acute phase proteins in the gingival crevicular fluid.[6] These have included α 2-macroglobulin, α1-antitrypsin and C-reactive protein, which are altered in the crevicular environment. Cytokines appear to play a major role in the clinical symptoms and tissue destruction associated with progressing periodontitis.[7]

Table 4 : Regulation of acute phase reactant production.[5]

Effectors	Response of acute-phase proteins
IL-1 type cytokines	Stimulation of type I acute-phase proteins. • C-reactive protein • α1-acid glycoprotein • Ceruloplasmin • Factor B • Serum amyloid A • Serum amyloid P protein • Haptoglobin (rat) • Hemopexin (rat) Inhibition of type II acute phase proteins
IL-6 type cytokines	Stimulation of most acute-phase proteins • Cysteine proteinase inhibitor • α2-macroglobulin • Fibrinogen • α1-proteinase inhibitor • Haptoglobin (human) • α1-antichymotrypsin • Ceruloplasmin • C1 esterase inhibitor • α1-antitrypsin Synergism with IL-1-type cytokines on type I acute-phase proteins.
Glucocorticoids	• Minor stimulation of most acute-phase proteins, strong stimulation of rat α1-acid glycoprotein • Strong synergistic enhancement of cytokine effects on most acute-phase proteins.
Insulin	• Reductions of IL-1-and IL-6-type cytokine effect on most acute - phase proteins.
Hepatocyte growth factor, fibroblast growth factor and transforming growth factor ß	• Minor reduction of IL-1- and IL-6-type cytokine effects on most acute-phase proteins. • Enhancement of IL-1-type cytokine effects on rat α1-acid glycoprotein and C3.
Hormones acting via cyclic nucleotides or calcium mobilization	• No detectable regulatory effect on acute-phase proteins.

Table 5 : Characteristics of acute-phase cytokines in the acute-phase reaction.[5]

	Name	Ligands	Source	Action
1	IL-1	IL-1α IL-1β IL-1Ra	Perturbations of the cell membrane Stimulating the macrophage.	Elicits systemic inflammatory reactions such as fever and the acute phase response of the liver.
2	TNF	IL-1α IL-1β	Mononuclear phagocytes activated cells Cytotoxic T cells	IL-1 like bone resorptive activity. Enhance resorption of proteoglycan. Induction of proliferation of fibroblasts.
3	IL-8		• Vascular and lung endothelium • Monocytes • Eosinophils • Fibroblasts • Keratinocytes • Kidney mesangeal cells • Astrocytes	Induce acute phase protein production

Table 6 : Key properties of cytokines linked to the acute-phase reaction.[5]

MEDIATOR	ACTIVITY
IL-1-type cytokines (IL-1α, tumor necrosis factor ß)	Prototype proinflammatory cytokines; stimulation of acute phase protein synthesis
IL-1Ra	Member of the IL-1 family; blocks binding of IL-1 to cell surface receptors; prototype anti-inflammatory cytokine
Soluble tumor necrosis factor receptor p55/p75	Naturally occuring tumor necrosis factor inhibitors; comprise extracellular domains of the two known tumor necrosis factor receptors, p55 and p75; block tumor necrosis factor-regulated inflammatory processes.
gp130 signalling cytokines (IL-6,IL-11, leukemia inhibitor factor, oncostatin M, ciliary neurotrophic factor, cardiotrophin)	Pro-and anti-infammatory activities, stimulation of most acute phase protein; induction of IL-1ra and soluble tumor necrosis factor receptor p55 in vivo; several anti-inflammatory effects in vivo and in vitro; evidence for anti-inflammatory activities in IL-6 knockout models

Table 7 : Characteristics of the acute phase reaction response molecules.[3]

Sl. No.	Name	Action
1.	C-Reactive protein	• Induce the synthesis of IL-1α, IL-1β, TNFα and IL-6. • Anti inflammatory role.
2.	Serum amyloid A	• Elevated during inflammation.
3.	α_2- Macroglobulin	• Modulates the activity of IL-1, IL-1β, TNF-β, TNF-α, TGF-β and PDG F.
4.	α_1- acid glycoprotein	• Increases during inflammation. • Immunoregulatory role.
5.	α_1-Antitrypsin	• Increases during inflammation.
6.	Hapatoglobulin	• Increases during infection or inflammation.
7.	Fibrinogen	• Accumulates at the site of injury and in the presence of enzymes released from PMNL and platelets, fibrin is found.
8.	Complement components	• Regulate the inflammatory response.
9.	Ceruloplasmin	• Copper transporting protein. • Transfers copper to cytochrome-C oxidase.
10.	Albumin and transferin	• Serum iron transport protein. • Decreased during inflammation. • Starve microorganisms of iron required for growth and virulence expression.
11.	Lipoprotein A	• Low density lipoprotein like particle. • Elevated plasma levels of lipoprotein A → risk factor for atherosclerosis.

The total amount of IL-1α and IL-1ß, but not total IL-1Ra were found to be correlated with alveolar bone loss score.[8]

In response to periodontal pathogens, neutrophils release oxidants, proteinases and other tissue destructive factors. The balance between these factors, the antioxidants, and endogenously synthesized antiproteinases (such as acute phase proteins) may determine the extent of periodontal damage. Since the acute phase response plays a central role in promoting healing, periodontitis as a wound healing problem would be directly affected.[9]

Differences in C-reactive protein and haptoglobin levels may distinguish a group of adult periodontitis subjects with more severe disease.[10] Measurement of acute-phase proteins could provide a valuable tool to identify changes in the periodontal health of the patients, particularly in the high risk subset of periodontitis patients. Due to the existing variability in serum, acute phase reactants within this adult periodontitis population, conclusions on the effect of treatment on these levels remains somewhat equivocal. Both mechanical oral debridement and treatment with nonsteroidal anti-inflammatory drug appeared to effect these serum glycoprotein markers of infection and inflammation.

The bacterial species reported to be important to periodontal disease progression and the formation of an inflammatory lesion stimulate the host to respond to these infecting bacteria by both specific and non-specific immune responses, as well as the release of reactive free radicals for phagocytes and a host of metabolic changes under the control of various cytokines. Chapple et al[11] determined that the total antioxidant activity in the serum of the healthy and periodontitis subjects were similar. However, the periodontitis subjects were found to have a reduced level of total salivary antioxidants compared with the healthy subjects. Therefore, alterations in the local environment may be essential to periodontal disease activity and may reflect increased levels of local radical production by local polymorphonuclear leukocytes and macrophages during disease progression.

Thus, the potential exists that the utilization of antioxidants as an intervention agent in maintaining the acute phase response as a homeostatic mechanism to control the chronic inflammation of periodontitis could have profound local and systemic implications.

Studies have also indicated a closer linkage of periodontitis with systemic manifestations of this chronic infection and inflammation.

Thus, the acute phase response might be useful as biomarkers of periodontitis contribution to systemic disease, as well as providing a potential mechanistic link between the local and systemic manifestations of periodontitis.

Of the numerous periodontal variables analyzed in this retrospective analysis, bone loss appeared to be the most consistent variable associated with coronary heart disease and thus, periodontal disease appeared to be associated with excess risk of cardiovascular disease and stroke. Periodontitis patients presented with increased levels of serum fibrinogen (an acute-phase protein) and elevated white blood cells, significant risk factors for coronary heart disease.[12] Genco et al[13] have provided preliminary data associating specific periodontal pathogens, immune responses and inflammation with the formation of atheromatous plaques and associated with cardiovascular disease.

The detection of acute-phase reactants in the serum of periodontitis patients suggests that noxious materials from the oral cavity may have the capacity to challenge various tissue and organ systems, in addition to the liver. Collins et al[14] reported that subclinical infections with periodontal pathogens induced low birth weight pups and this appeared to be associated with increase in intra amniotic prostaglandin E^2 and tumour necrosis factor α.

Summary and conclusion

The oral disease, Periodontitis, has for many years been considered a disease confined to the oral cavity. It is only in the past several years that substantial scientific data have emerged that indicate that the localized infections characteristic of periodontitis can have a significant effect on the systemic health of both humans and animals.

Oral infections produce significant increase in systemic inflammatory responses, manifested by acute-phase cytokines and acute-phase reactants. Therapeutic oral manipulations or the inappropriate or absence of intervention of progressing periodontitis could have a significant influence on these systemic diseases. Therefore, an understanding of the relationship between the progression of periodontitis and risk factors associated with cardiovascular disease (such as diet, serum lipids, acute-phase responses, etc.,) and other systemic health complications (such as low birth weight infants, diabetes and systemic inflammatory diseases) would have a profound effect on the strategies for treatment of the periodontal diseases. Finally, the substantial role of free radicals in periodontitis and their effects on the suppression of antioxidant defenses and the acute-phase responses should provide important information relevant to drawing parallels between periodontitis and systemic health complications.

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