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Diagnostic Value of Acute Phase Proteins in Periodontal, Psychosomatic and Cardiometabolic Diseases: Response to Treatment

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1. Introduction

The host response to bacterial plaque biofilm on tooth surfaces initiates periodontal disease and its progression affecting the supporting structures of teeth. Stressor responses of the host to plaque biofilm result in markers of inflammation that are common to diabetes mellitus and coronary heart disease (Pussinen et al 2007). These inflammatory markers are relevant to periodontitis, anxiety states, associated systemic diseases and their sequelae in a bi-directional manner. The extent and clinical significance of these associations have received increasing coverage in the literature. This is largely dependent on the scale of the inflammatory loading based on the severity of periodontal inflammation at the time of examination and the number of sites involved (Norse et al 2008). Response to periodontal treatment with decreased levels of serum markers is indicative of the importance of this source of systemic inflammatory loading. The impact of inflammatory loading from the periodontium as a significant source of systemic inflammation has been an area of debate.
The extent and severity of periodontal inflammation in the presenting population determine its significance in this context. It has wider implications in the context of co-morbidities in periodontal patients. In addition to the commoner co-morbidities, coronary heart disease (CHD), diabetes mellitus and arthritis, other autoimmune conditions and anxiety states also show similar links. This chapter aims to provide such evidence, conflicting at times due to multifactorial presentations of clinical conditions and individual susceptibility. In relevant cases, given a sufficient impetus from inflammatory loading it highlights the importance of controlling periodontal disease in a systemically-ill population. Searches were done over the past 10-15 years, using keywords relevant to the title; subsequently limited to those representing key information focusing on inflammatory markers, their significance and relevance to periodontal, psychosomatic and cardiometabolic diseases with implications on treatment.

This included a systematic review and meta-analysis of C-reactive protein (CRP) in relation to periodontitis, a general overview of the acute phase reaction in infections and inflammatory diseases as the main core, using objective selection criteria and a comprehensive database (Pub Med, Science direct, Wiley-Blackwell, Springer and Ovid-Medline). Several putative risk factors/indicators involved in periodontal disease progression with emphasis on those associated with altered immune mechanisms such as markers of stress/ anxiety states, markers of periodontal disease and relevance of cardiometabolic disorders and autoimmune diseases have been discussed in the context of treatment responses, throughout the text. The search was limited to the last 10 – 15 years including reviews and original research in the subject areas of relevant acute phase reactions and their role in the progression of periodontitis, treatment responses and association with cardiometabolic disorders; and documentation was selected to represent the theme and provide insight in key areas of relevance.

Key words and phrases used for searches include: 1. Psychological stress; acute phase proteins, 2. Periodontitis; cardiometabolic diseases; atherosclerosis; periodontal treatment, 3. Risk factors; atherosclerosis; inflammation; periodontitis; treatment response, 4. Biomarkers; periodontitis; cardiovascular disease, 5. Periodontal disease; psychology; stress, 6. Inflammatory cytokines; periodontitis; atherosclerosis, 7. Aggressive periodontitis; C-reactive protein; IL-6, 8. Psychosomatic factors; stress; anxiety and periodontal disease.

The main objectives and key questions asked are:

1. The effects of psychological stress on acute phase protein profiles in periodontitis patients.
2. Are CRP levels significantly elevated in periodontitis patients and what is the effect of periodontal therapy?
3. What are the potential mechanisms implicated in the association between periodontitis and cardiometabolic disorders; and the effect of periodontal treatment on markers of coronary arterial, peripheral arterial and metabolic diseases?

The above theme has been addressed in the context of diagnostic and therapeutic relevance.

2. Anxiety states and periodontal disease

Stress-induced neurohormones play a critical role in the outcome of infections. Neuro-immune-endocrine interactions in response to stress could affect periodontal disease progression. Catecholamines (epinephrine and norepinephrine) stimulate the formation and activity of prostaglandins and proteolytic enzymes, which can indirectly produce tissue destruction. The relationship between stress and periodontal disease could be mediated by alteration in gingival crevicular interleukins, depressed polymorphonuclear leukocyte chemotaxis and phagocytosis and reduced proliferation of lymphocytes upon stimulation by a mitogen. Anxiety states could dysregulate neuro-endocrine regulatory mechanisms involved in immune regulation and thereby alter immune responses influencing the development and progression of infections and inflammatory diseases including periodontitis; with potential impact on bone density and osteoporotic changes via immune and endocrine mechanisms. Determination of levels of anxiety states in relation to disease markers would clarify cause and effect relationships in psychosomatic diseases.

Variation in severity of periodontal disease cannot be explained by a limited number of risk factors (Teng et al 2003). Associations between stress-inducing factors and periodontal disease have been examined in several studies (Wimmer et al 2002, Pistorius et al 2002).

Periodontal disease is more widespread and severe in subjects with higher levels of stress. Effects of various psychological and psychosocial factors such as emotional and other sources of stress have been the focus of documentation in the context of oral diseases. There are correlations between psychological factors and advanced periodontal disease (Wimmer et al 2002) with unfavourable effects on the progression of periodontal diseases (Pistorius et al 2002). A great deal of evidence suggests that stress-induced neurohormones play a critical role in the outcome of infections (Aviles et al 2004; Sonnenfeld et al 2002; Belay and Sonnenfeld 2002; Lyte 2004). Individual susceptibility factors could affect disease outcome and account for the variations seen.

Glucocorticoids released in the cortex of the suprarenals induce reduced secretion of pro-inflammatory cytokines such as interleukins (IL), tumour necrosis factor (TNF) and also prostaglandins. On the other hand, catecholamines (epinephrine and norepinephrine) have the opposite effect, stimulating the formation and activity of prostaglandins and proteolytic enzymes, which can indirectly produce tissue destruction. Several studies have explored the associations among stress, salivary cortisol, and periodontal disease (Rosania et al 2009; Johannsen et al 2006; Hilgert et al 2006). The relationship between stress and periodontal diseases could be mediated by alteration in gingival crevicular IL levels (Deinzer et al 1999; Mengel et al 2002; Giannopolou et al 2003; Kamma et al 2004), depressed polymorphonuclear leukocyte (PMN) chemotaxis, phagocytosis, and reduced proliferation of lymphocytes upon stimulation by a mitogen. Other possible mechanisms could involve changes in gingival circulation, alteration in salivary flow, its components and possible endocrine changes (Sheiham & Nicolau 2005). Raised serum and tissue levels of noradrenaline in patients subjected to stress could affect the composition or phenotype of subgingival periodontal pathogens.

Recent studies suggest that stress and depression may affect the onset and progression of periodontal disease through behavioral and physiologic mechanisms (Peruzzo et al 2007; Rosania et al 2009). Depression may dysregulate cerebral homeostatic mechanisms involved in immune regulation, and thereby influence the initiation and progression of infections and inflammatory diseases, including periodontitis (Pavlov & Tracey 2004; Behl et al 2008). Antidepressant treatment contributes to immune regulation in patients with major depressive disorders (Maes 2001). Venlafaxine and fluoxetine were found to exert negative immunoregulatory effects by inducing a change in lymphocyte subsets and by suppressing the interferon-γ and interleukin-10 production ratio in whole-blood cells (Kubera et al 2001; Basterzi et al 2009).

There is extensive documentation of individuals under psychological stress being more susceptible to loss of periodontal attachment and alveolar bone. Social stressors could contribute to glucocorticoid resistance and increased production of IL-1β, IL-6 and TNF-α (Powell et al. 2005), as a result of stressor-induced dysregulation of CD11b+ monocyte activity in response to microbial products (Bailey et al 2009). There is increased toll-like receptor-driven nuclear factor-kappa B (NF−κB) activity (Padgett and Glaser 2003). This could exacerbate periodontal and systemic inflammation, insulin resistance and hypertension, predictive of vascular impairment. Human stress-response studies of peripheral blood leukocytes show under-representation of genes activated by glucocorticoids which serve to suppress the immune response and an over-representation of genes regulated by NF-κB, usually suppressed by glucocorticoids. Some of these mechanisms could explain the strong psychosomatic implications of stress on periodontal

disease (Hilgert et al 2006; Genco et al 1999; Ishisaka et al 2008; Ishisaka et al 2007). Other possible mechanisms include modification of patients' health behavior. Individuals with high levels of stress tend to adopt habits that are harmful to periodontal health, such as negligent oral hygiene, increased smoking or changes in dietary habits (Deinzer et al 1999) and the outcome my be modified by genetic predisposition.

Studies have reported an association between depression and low bone mineral density. Depression may induce bone loss and osteoporotic fractures, primarily via specific immune and endocrine mechanisms, while use of specific antidepressants such as the selective serotonin re-uptake inhibitors (SSRIs) are potential contributory factors (Cizza et al 2009). These factors could play a secondary role in the progression of periodontitis in patients thus afflicted.

2.1 Concept of markers for periodontal and systemic diseases, relevant to anxiety states

Based on the psychosomatic interactions discussed, markers which allow identification of susceptible individuals prior to the onset of periodontitis, have evolved. There is increasing recognition of risk factors that might be modified in order to prevent or alter the course of periodontal disease (Van Dyke 2005). An analysis of systemic and microbial factors in epidemiological studies points to several risk factors associated with periodontitis. These factors include local, systemic, demographic, and behavioural host conditions which markedly affect the resistance to infecting pathogens (Albander 2002; Genco 1999). They may be considered to be associations which amplify or abate responses but not necessarily causative. Non-environmental intrinsic factors such as genetic make-up, are not modifiable (Van Dyke 2005), but may be influenced by environmental and behavioural factors.

Associations have been established between chronic periodontitis, caused by unresolved inflammation (Pihlstrom et al 2005), and an increased risk of coronary artery disease where inflammation appears to be the main factor (Gibson lll & Genco 2007; Gibson lll et al. 2008; Paoletti et al. 2004). Interestingly, both disease entities have been associated with the stress response.

Individuals under psychological stress are more likely to develop clinical attachment loss and associated alveolar bone loss (Hugoson et al 2002; Mawhorter & Lauer 2001; Pistorius et al 2002; Wimmer et al 2002). One possible link in this regard may be increases in production of IL-6 in response to increased psychological stress (Kiecolt-Glaser et al 2003). IL-6 induces the expression of CRP, an acute-phase reactant responsible for the increase in expression of cellular adhesion molecules and vascular inflammation. Based on the biological properties of these pro-inflammatory cytokines, high plasma levels of TNF-α and IL-6 have been associated with an increased risk for developing cardiovascular events, morbidity and mortality (Abeywardena et al 2009; Ryan et al 2009). Periodontal diseases seem to act as a source of pathogenic species, virulence factors and inflammatory mediators that are conveyed systemically, creating and sustaining a chronic systemic inflammatory burden (Haraszthy et al 2000; De Nardin 2001; Beck & Offenbacher 2005). The magnitude of this inflammatory burden would depend on the degree of inflammation present at the time of examination. It has also been suggested that peripheral blood monocytes from periodontitis subjects may present a distinct profile of inflammatory mediator release in response to bacterial challenge when compared with healthy subjects (Sorensen et al 2009; Yamaguchi et al 2009).

Periodontal symptoms can be exacerbated during periods of stress, and stress could potentially increase the risk of developing coronary heart disease (Dimsdale 2008), along the mechanisms detailed above, depending on individual susceptibility factors. As a result, a thorough understanding of the diverse ways in which inflammation can be regulated is imperative in order to execute effective management to control inflammatory diseases.

In response to a stressor, host responses which provide a buffering effect are triggered. Chronic activation of stress responses results in chronic release of glucocorticoids and catecholamines due to activation of the hypothalamic-pituitary-adrenal- and sympathetic-adrenal-medullary axes. Glucocorticoids expressed in host immune cells bind cortisol and interfere with NF-kB-regulated functions of host cells which produce cytokines. The role of stress in contributing to immune dysregulation and the mechanisms involved have been reviewed (Padgett & Glaser 2003). Genes encoding for a variety of cytokines are induced by adrenergic receptors binding epinephrine and norepinephrine via a cAMP response element binding protein, a cellular transcription factor. Glucocorticoids and catecholamines mediate changes in gene expression which could cause immune dysregulation. There is good documented evidence from animal and human studies of the significant impact of stress-associated immune dysregulation on health.

2.2 Effects of stress on inflammation: Role of cytokines as a source of inflammatory loading

Psychological stress increases the expression of markers of peripheral inflammation. There is increasing evidence of an association between periodontal pathogens and systemic inflammation. The impact of social disruption (SDR) as a social stressor was investigated in mice in response to LPS derived from the periodontal pathogen *Porphyromonas gingivalis (Pg*) (Bailey et al 2009). Following consistent exposure to SDR over 6 days, mice were tested for anxiety-related behaviour and sacrificed. Harvested spleen cells were stimulated with *Pg*-derived LPS in the presence or absence of increasing doses of corticosterone. SDR-induced anxious behaviour was associated with the production of significant amounts of IL-1β and TNF-α, when compared with non-stressed control mice. Cultures enriched for CD11b+ cells indicate that splenic myeloid cell activity is affected by social stress. The inflammatory response to oral pathogens could play an important role in stress-associated systemic inflammation.

The social stressor SDR induces an increased inflammatory response and glucocorticoid resistance in CD11b+ monocytes. Splenic dendritic cells (DC) from SDR mice displayed increased levels of MHC1, CD80 and CD44 indicating an activated phenotype, compared with controls. Increased amounts of TNF-α, IL-6 and IL-10 are produced by DCs from SDR mice, compared with controls (Powell et al 2009). Previous work has shown glucocorticoid resistance in DCs from SDR mice. This is suggestive of DC activation by social stress in the absence of an immune challenge, with increased cytokine secretion in response to toll-like receptor activity and glucocorticoid resistance.

SDR, a murine model of social stress alters the phenotype and actions of splenic immune cells. In response to SDR, splenic CD11b+ monocytes are increased in number and are less sensitive to the negative effects of glucocorticoids on cell viability. Greater amounts of the inflammatory cytokines TNF-α and IL-6 were secreted by spleen cells from SDR mice in response to LPS, compared with controls. Secretion of TNF-α was increased by SDR in an enriched fraction of CD11+ monocytes stimulated by LPS (Avitsur et al 2005). The kinetics

of TNF-α release in these cells are also altered with minor changes in attenuation of LPS-induced TNF-α secretion in response to corticosterone and norepinephrine. Responses to social stress are determined by complex immunomodulatory mechanisms which could have a varied impact on individuals, based on genetic and other environmental factors.

Both IL-1β and TNF-α are known to be important in the development of oral inflammatory diseases such as gingivitis and periodontitis; elevated levels of these cytokines have been isolated in periodontal patients at the site of active tissue breakdown (Gamonal et al 2003; Orozco et al 2006). These cytokines have diverse effects on gingival tissue, such as degradation of connective tissue matrix via an increase in matrix metalloproteinases, and activation of osteoblastic/osteoclastic responses via disruption of the balance between physiological repair and remodelling (Graves & Cochran 2003). Elevated cytokine levels, however, are not limited to the infected gingiva, and people with chronic periodontitis have been found to have increased levels of cytokines in the circulation, including IL-1β and TNF-α (Golub et al 2006). These circulatory cytokines are not likely to be the result of "spillover" from the infected gingiva, but rather, derived from peripheral cytokine producing cells, such as CD11b+ macrophages present in reticuloendothelial organs (i.e., the spleen, liver, and lungs), which are capable of producing high levels of inflammatory cytokines upon encountering *Pg* or its lipopolysaccharide (LPS).

Oral bacteria and bacterial derived products can enter the bloodstream via standard oral hygiene procedures and periodontal treatment (Kinane et al 2005) as well as through pathogen-induced ulceration and vascular permeability in the gingivae (Gibson lll et al 2008). As they circulate systemically, microbial products are recognized by cells of the reticulendothelial macrophages and other innate immune cells. These cells are able to respond to *Pg* and *Pg*-associated products, by producing a variety of inflammatory mediators, including the inflammatory cytokines IL-6, IL-1, TNF-α and CRP (Pussinen et al 2007a). These inflammatory mediators are considered to be the link between oral inflammatory diseases and associated systemic conditions.

Inflammatory loading from periodontal disease could contribute to the progression of cardiometabolic and autoimmune diseases which are driven by inflammatory mechanisms leading to oxidative stress-induced tissue and organ damage (Pussinen et al 2007b). The bidirectional relationship between periodontal disease and diabetes mellitus is well documented. Serum markers of periodontitis are derived from periodontal pathogens and host defence mechanisms. Elevated levels of serum LPS derived from periodontal pathogens, antibodies to LPS and LPS binding protein are detected in periodontitis compared with periodontally healthy subjects. Surrogate markers of immune-mediated responses to plaque antigens such as antibodies, MMPs, cytokines and markers of inflammation are detected. Antibodies to periodontal pathogens are indicative of systemic exposure to this antigenic stimulus. Serum screening methods for detection of markers for periodontitis would be useful in correlating with inflammatory markers from systemic diseases. The scale of inflammatory loading from periodontal disease would largely determine its impact on systemic diseases. This could account for variations in clinical presentation and response to treatment.

3. Acute phase proteins (APPs)

The APPs are synthesized and released from the liver and have a tendency to increase in response to various stimuli, including tissue injury and surgical stress. Activation of the

sympathetic nervous system, hypothalamic-pituitary axis and the renin-angiotensin system, results in the release of various stress hormones.

An acute phase response is similar to that associated with inflammation, which is characterized by macrophage activation, the production of cytokines, other inflammatory mediators, APP, and mast cell activation, all of which promote inflammation (Black and Garbutt 2002). IL-1, released from macrophages activated at the site of injury appears to be the most important factor in this response. IL-1 initiates a variety of systemic reactions, including the production of APP by hepatocytes. C-reactive protein (CRP), alpha-1-acide glycoprotein (AAG), ceruloplasmin (CER), haptoglobulin (HPT), and alfa-1-antitrypsin (AT) have been shown to be APPs. Serum levels of the acute phase protein AAG, are elevated in response to a variety of acute and chronic inflammatory stimuli. Its function is unclear, but is used as an indicator of the acute phase response (Mc Pherson 2001). Recent documentation demonstrates the importance of CRP and cytokines such as IL-6 and TNF-α amongst others, in untreated chronic periodontal disease and their association with systemic diseases as effective markers of inflammation, showing reduction with disease control.

3.1 Implications of CRP and cytokines on periodontal and systemic diseases

A thorough understanding of diverse means of regulation of inflammation is imperative for effective control and treatment of inflammatory diseases. A spectrum of inflammatory mediators, including CRP, the inflammatory cytokines IL-6, IL-1β and TNF-α are thought to provide a link between periodontal and systemic diseases (Craig et al 2003). Periodontal disease is more prevalent and severe in subjects with greater levels of stress, associated with psychological and psychosocial factors (Hugoson et al 2002), affecting its progression and response to treatment.

CRP is one of the major acute-phase proteins synthesized in response to pro-inflammatory cytokines. The concentration of CRP increases with inflammation. Recently, CRPs have been found to activate complement in damaged vessel walls and to promote the formation of foam cells during the initiation of atheroma formation. IL-6 is an important activator of CRP production and is a key pro-inflammatory and immune-modulatory cytokine, secreted mainly by monocytes, macrophages and T lymphocytes recruited to sites of infection or inflammation. The pro-inflammatory and pro-coagulant properties of IL-6 are likely to play a significant role in the pathogenesis of coronary syndromes. The elevation of CRP and IL-6 suggests a plausible biological mechanism underlying the association between periodontitis and cardiovascular diseases (Ridker 2003).

Several parameters of systemic inflammation have been linked with CHD and diabetes. For example, serum levels of CRP are increased in diabetic patients and CRP has been shown to be a strong predictor of cardiovascular events, with reduced levels following periodontal treatment (Hussain-Bokhari et al 2009); elevated levels of IL-6 in peripheral blood have been associated with unstable angina and metabolic dysregulation. Periodontitis is associated with elevated systemic levels of CRP and IL-6. As periodontal infections may increase the risk of atherosclerosis and poor glycemic control in diabetic patients, it is postulated that CRP andIL-6 are some of the mediators involved in the association between periodontitis and cardiometabolic disorders (Freeman et al 2002).

Inflammation plays a pivotal role in destructive periodontitis and atherosclerotic complications, which could be exacerbated by stress (Dimsdale 2008). CRP, monitored as a major risk factor for complications of atherosclerosis, also demonstrates raised levels in

periodontitis. Mean CRP is shown to be elevated significantly in subjects with extensive periodontal pocketing in comparison with those with shallower probing pocket depths. Body mass index (BMI) modifies the association of extensive periodontal disease with CRP. A BMI of 20 is predictive of a 2-fold difference in mean CRP levels between deep and shallow periodontal pocket groups (Slade et al 2003). This would be a relatively simple and effective tool for advising patients on improving periodontal and systemic health at baseline and in response to treatment.

It has been demonstrated that several parameters of systemic inflammation are associated with cardiovascular diseases and diabetes. For example, CRP has been shown to be a strong predictor of cardiovascular events, and the levels of CRP are increased in the serum of diabetic patients (Ridker 2003; Freeman et al 2002). In addition, elevated levels of IL-6 in peripheral blood have been associated with unstable angina and metabolic dysregulation (Biasucci et al 1996; Vozarova et al 2001).

Furthermore, periodontitis has been related to the elevation of systemic levels of CRP and IL-6 (Loos et al 2000; Yamazaki et al 2005; Noack et al 2001). As periodontal infections may increase the risk of atherosclerosis and poor glycemic control in diabetic patients (Beck et al 2005; Taylor et al 1996), it is postulated that CRP and interleukin-6 could be possible mediators involved in the association between periodontitis and systemic diseases.

CRP is one of the major acute-phase proteins, synthesized primarily in the liver in response to pro-inflammatory cytokines. The concentration of CRP increases with inflammation (Gabay and Kushner 1999). These acute phase proteins are known to activate complement in damaged vessel walls and to promote the formation of foam cells during the initiation of atheroma formation (Torzewski et al 2000; Du Clos 2000). IL-6 is an important activator of CRP production (Steel and Whitehead 1994) and is a key pro-inflammatory and immune-modulatory cytokine, secreted mainly by monocytes, macrophages and T lymphocytes recruited to sites of infection or inflammation. IL-6 has pro-inflammatory properties and procoagulant effects, and these properties are likely to play a role in the pathogenesis of coronary syndromes (Maseri et al 1996).

The elevation of CRP and IL-6 suggests a plausible biological mechanism underlying the association between periodontitis and cardiovascular diseases. Several inflammatory signals and markers including high sensitivity CRP (hsCRP), cytokines such as IL-1, IL-6 and TNF-α which are reported to be associated with periodontitis are also involved in atherothrombogenesis (Ridker et al 2000; Ridker & Silvertown 2008). An elevation of CRP is regarded as a biomarker of systemic inflammation and as a risk marker for CVD (Ridker 2003); hsCRP has been shown to be the strongest biomarker for predicting cardiovascular events. A recent meta-analysis of 10 cross-sectional studies showed that CRP in periodontitis patients is elevated in comparison with controls without periodontitis (Paraskevas et al 2008). In addition, the presence of *Pg* in periodontitis patients is associated with increased CRP levels, suggesting that elimination of this periodontal pathogen could reduce serum CRP levels (Pitiphat et al 2008).

Other biomarkers significantly associated with the risk of cardiovascular events are serum amyloid A, sICAM-1, IL-6, homocysteine, total cholesterol and low density lipoprotein (LDL) cholesterol (Ridker et al 2000). Among them, serum levels of IL-6 in the upper quartile of the considered normal range are independently predictive of an increased risk of premature death or future myocardial infarction, even after accounting for CRP levels in large prospective studies of healthy populations (Nakamura et al 2008). IL-6 is also a marker for identifying patients with unstable coronary artery disease independent of other risk

indicators. It is relevant that both periodontal and coronary heart disease populations share similar risk factors in this context.

4. Associations of periodontal disease with coronary heart disease

A possible association of periodontal disease with coronary heart disease (CHD) has received attention in the literature, demonstrating a raised antibody titre to periodontopathic bacteria in CHD patients compared with healthy controls. When serum antibody levels in response to 12 periodontal pathogens were investigated amongst patients with CHD and moderate to severe periodontitis, the antibody response was most prevalent for *Pg* a major causative pathogen implicated in CHD as well as periodontitis (Yamazaki et al 2007). When the antibody response to two different strains *Pg* FDC381 and Su63 was analysed, periodontal patients were positive for both strains while CHD patients showed an elevated response to *Pg* Su63 but not for the *Pg* FDC381 strain. These findings demonstrate that periodontal pathogens with high virulence may affect atherogenesis; knowledge of the virulence factors of *Pg* Su63 could open new therapeutic modalites for *Pg*-associated atherosclerotic changes. DNA of *Pg* has been detected in atherosclerotic plaque suggestive of bacteraemias and endotoxaemias during the progression of periodontitis (Pussinen et al 2007a; Forner et al 2006; Nakano et al 2008). Direct effects of periodontopathic bacteria on host cells could contribute to the link between periodontitis and coronary heart disease (Schenkein et al 2000). A cause and effect relationship based on these concepts would be determined by the size of the inflammatory loading, genetic and environmental factors.

Destructive periodontal disease is associated with increased risk of atherosclerotic complications. Inflammation plays a pivotal role in periodontitis and atherosclerosis. CRP an acute phase protein monitored as a major risk factor for complications of atherosclerosis, also demonstrates raised levels in periodontitis. The effect of periodontal disease progression (>2mm attachment loss, 2 months post-baseline) on the acute-phase response has been investigated (Craig et al 2003). ELIZA (enzyme-linked immunosorbent assay) was used for measuring serum antibody and a high sensitivity (hs) CRP assay was used to measure CRP. Results indicated that periodontal disease status, severity and progression; also male gender and smoking were associated with serum IgG antibody to *Pg* rather than 5 other species. LDL cholesterol increased in disease, while HDL increased in health. Regression analysis indicated a correlation between IgG antibody to *Pg* and age, probing depth and hsCRP. Multiple sites of disease progression and raised antibody titre to *Pg* increased the odds ratio for elevated levels of hsCRP. It was concluded that destructive periodontal disease and its progression are characterized by an acute phase-response associated with relevant serum markers. These events are similar to those seen in cardiometabolic disorders, underscoring the impact of periodontal disease progression on systemic diseases in view of the contribution of extensive periodontal disease and BMI to raised CRP levels in susceptible subjects. Also highlighting the importance of cardiometabolic disorders in periodontal patients in evaluating the source of acute phase proteins and a bi-directional impact of treatment, beneficial in controlling both periodontal and systemic diseases.

Documented literature indicates the importance of periodontal disease as an inflammatory exposure relevant to the progression and outcome of systemic diseases in addition to being a disease entity with its own outcome. Clinical, microbiological and inflammatory components indicate risk for systemic diseases, associated with an inflammatory burden

and its sequelae. These may not necessarily be the same parameters used to define periodontal disease. Temporal relationships between exposure and disease outcome are also relevant. Clinical parameters of periodontal disease have been correlated with serum levels of 2 systemic risk markers of cardiovascular disease, soluble intercellular adhesion molecule (sICAM) as a measure of vascular stress and serum CRP as a measure of an acute phase response (Beck & Offenbacher 2002). This was part of a cross-sectional study of the relationship between periodontal disease and cardiovascular disease in the Dental Atherosclerosis Risk in Communities (ARIC) study. It is relevant that while attachment loss, probing depth (PD) and bleeding on probing (BOP) were individually associated with sICAM and CRP, only BOP was significant for sICAM when all 3 were included in the model; PD was significant for CRP. Both clinical parameters PD and BOP are more robust in estimating the extent of systemic inflammation than categorization of early, moderate and severe periodontal disease based on bone support or attachment loss which may not correlate with the extent of inflammation at the time of examination. A tooth centered approach to periodontitis may not fit the mould of systemic inflammation where relevant parameters such as PD and BOP would fit the underlying mechanisms and temporal sequelae affecting systemic outcome of periodontal inflammation. Study design and parameters measured could account for some discrepancies in the reported literature, on systemic markers for periodontal and cardiometabolic disorders and response to treatment in this context.

In view of the association between systemic levels of the inflammatory markers CRP, fibrinogen and WBC with a risk of CHD, also demonstrated for periodontal disease, the effect of periodontal treatment on these systemic parameters has been investigated in subjects with or without CHD. The periodontal paramenters, bleeding on probing (BOP) and probing depths (PD) were measured in subjects with or without coronary heart disease (Hussain-Bokhari et al 2009). All subjects received non-surgical periodontal therapy including plaque control measures and thorough root surface debridement. There were significant reductions in BOP, PD and systemic inflammatory markers in both groups after periodontal therapy. This could contribute to decreased risk for CHD in treated periodontal patients. This profile is valuable in the planning of large-scale intervention trials to reduce risk for CHD with periodontal intervention.

Non-surgical periodontal treatment for periodontal pocket reduction induces systemic changes in several biochemical markers that reflect the risk for atherosclerosis. In a study where successful periodontal treatment with pocket reduction was reported in adult periodontal patients with severe periodontitis, serum glucose, lipids and markers of systemic inflammation were not significantly altered after 3 months. At one year, HDL-C concentrations were significantly increased and LDL-C concentrations decreased with concurrent reduction in IL-18 and interferon δ levels (Buhlin et al 2009). Both mechanical periodontal debridement and treatment with a nonsteroidal anti-inflammatory drug appeared to affect serum glycoprotein markers of infection and inflammation. Steroids and disease-modifying anti-rheumatic drugs are also effective in reducing levels of CRP by 30–70% which have implications for periodontal disease progression in patients presenting with co-morbidities. The results of some studies indicate that nonsteroidal anti-inflammatory drugs had minimal effects on CRP, although others have reported that flurbiprofen decreased CRP levels in a subset of patients. A change of 150% (CRP) or 70% (haptoglobin) in the levels of these acute-phase reactants indicate significance in the context of individual subject variation.

5. Periodontitis and dyslipidaemia

5.1 Psychosomatic aspects of obesity

There is growing evidence in the recent literature that obesity and periodontitis may be triggered or exacerbated by adverse social factors and certain psychological pathologies, traits and behaviors. Dental practitioners should therefore give consideration to the fact that overweight patients who present with impaired periodontal status may also be experiencing anxiety, depression, and impaired satisfaction with life.

Although periodontal disease is affected by behaviour determined by social and psychological factors, periodontists have not seriously considered psychosocial pathways in its etiology, diagnosis, and treatment. However, a sound understanding of the psychosocial pathways of behavior strongly linked to periodontal disease, and mechanisms whereby psychological factors affect the response of periodontal tissues to pathogens, is essential for diagnosis and improving the effectiveness of interventions (Sheiham & Nicolau 2005); which could also affect impact on co-morbidities.

5.2 Mechanisms affecting dyslipidaemia, diabetes and periodontitis

The inflammatory loading from periodontal disease could compromise cardiometabolic and autoimmune diseases which are driven by inflammatory mechanisms leading to oxidative stress-induced tissue and organ damage. The bi-directional relationship between periodontal disease and diabetes mellitus is well documented. Serum markers of periodontitis are derived from periodontal pathogens and host defence mechanisms. Elevated levels of serum lipopolysaccharide (LPS) derived from periodontal pathogens, antibodies to LPS and LPS binding protein are detected in periodontitis compared with periodontally healthy subjects; and surrogate markers of immune mediated responses to plaque antigens such as antibodies, matrix metalloproteinases, cytokines and markers of inflammation. Antibodies to periodontal pathogens are indicative of systemic exposure to this antigenic stimulus. Serum screening methods for detection of markers for periodontitis would be useful in correlating with inflammatory markers from systemic diseases.

Several parameters of systemic inflammation have been linked with CHD and diabetes. For example, serum levels of CRP are increased in diabetic patients and CRP has been shown to be a strong predictor of cardiovascular events; elevated levels of IL-6 in peripheral blood have been associated with unstable angina and metabolic dysregulation. Periodontitis is associated with elevated systemic levels of CRP and IL-6. As periodontal infections may increase the risk of atherosclerosis and poor glycaemic control in diabetic patients, it is postulated that CRP and IL-6 are some of the mediators involved in the association between periodontitis and cardiometabolic disorders.

Plasma fatty acids, an important cardiovascular biomarker, showed an altered profile, particularly when concentrations were measured in periodontitis patients, who presented with higher amounts of total fatty acids, saturated fatty acids, MUFA, and n-6 PUFA than controls. Dietary fat may affect immune responses and determine susceptibility of lipoprotein to oxidation, which affects the activation of adhesion molecules and other inflammatory agents (Von Schacky & Harris 2007).

Recently, a new association between lipid peroxidation, oxidative stress and periodontitis has been suggested and it is also related to the clinical periodontal status (Bullon et al. 2008). Evidence suggests an association between inflammatory markers, such as interleukins, oxidative stress-related parameters, and CHD events. It has been hypothesized that CHD

may be triggered by systemic mechanisms, in addition to local inflammatory factors, and chronic periodontal infection is one of the possibilities to be considered. Here, this hypothesis is fully supported by reported results on oxidative stress status, fatty acid profile, inflammatory interleukines and adhesion molecules. Indeed, the high correlations found between plasma triacylglycerols, LDLc, saturated fatty acids, polyunsaturated fatty acids, total amount of fatty acids and coenzyme Q10; with some periodontal data such as probing depths, gingival margin location and clinical attachment levels, leads to the conclusion that there is a close association between periodontitis, plasma fatty acids profile and an increase in metabolic risk factors for CHD.

Periodontal treatment influences blood lipid levels in a manner which is consistent with a decreased risk for CHD. HDL-C concentrations increased and LDL-C concentrations decreased significantly (Pussinen et al 2004). Previous intervention studies suggest that periodontal treatment decreases the levels of inflammatory markers such as CRP, fibrinogen and IL-6 (Pussinen et al 2004; Montebugnoli et al 2005). However, these studies were fairly small and the follow-up periods were only between 3 and 6 months. It would be important to carry out large scale, long-term studies on this theme considering the potential impact of controlling periodontal disease progression on coronary heart disease.

The predictive and prognostic value of CRP and fibrinogen as risk factors for cardiovascular disease is well-documented and could be used to stratify patients for this purpose. Moreover recent data is also suggestive of a primary role for insulin resistance in the pathogenesis of metabolic syndrome and prediction of cardiovascular events. Glycaemic indices could function as significant markers of the incidence of new cardiac events in subjects who may not be diagnosed diabetics. Although the traditional markers, reduced HDL-c, elevated LDL-c, triglycerides and visceral adiposity are associated with insulin resistance, it may independently influence the progression of coronary atherosclerotic plaques in asymptomatic patients, via endothelial dysfunction. Insulin resistance seems to have a significant prognostic role and informative for preventive care in acute coronary syndrome (Caccamo et al 2010). These mechanisms could impact on periodontal disease progression and therapeutic targets.

A common pathological pathway associated with systemic inflammation and insulin resistance link cardiometabolic disorders (Pischon et al 2007; Saito & Shimazaki 2007). The non-glycosylated polypeptide leptin synthesized primarily by adipocytes has several regulatory functions, with increased production during inflammatory responses. Its dual characteristics as a hormone and a cytokine provide a link between neuroendocrine and immune systems. It plays an important role in the pathogenesis of autoimmune inflammatory conditions such as diabetes (Lago et al 2008; Soory 2010a) and rheumatoid arthritis (Otero et al 2006; Soory 2010b). Metabolic syndrome is diagnosed in individuals with a risk of cardiovascular disease, comprising a cluster of abdominal obesity, hypertension, impaired glucose tolerance, hyper-insulinaemia and dyslipidaemia (Eckel et al 2005).

A significant relationship between oxidative stress and metabolic syndrome has been demonstrated in humans when compared with normo-lipidaemic subjects. Systemic oxidative stress and insulin resistance have been shown to correlate with attenuated antioxidant capacity. The effects of a hyper-inflammatory state seen in severe uncontrolled periodontitis and its impact on organs distant from the focus of inflammation are well documented in the context of oxidative stress-inducing mechanisms and the role of antioxidants (Soory 2009). Several cytokines are involved in the mediation of insulin

resistance, TNF-α in particular (Tilg and Moschen 2008). In the context of substances derived from oxidative damage, plasma lipid peroxidation plays an important role in the diabetic periodontal patient (Sonoki et al 2006) with decreased lipid peroxidation following periodontal therapy. The pathogenesis and progression of periodontal disease is escalated by advanced glycaemic end products AGE (Takeda et al 2006), receptor for AGE (RAGE) which is highly expressed in periodontal tissues and AGE/RAGE interactions in uncontrolled diabetics. Using a diabetogenic cell culture model of well characterized osteoblasts, it has been demonstrated that the oxidative effects of AGE and nicotine were overcome by the antioxidant glutathione (Rahman & Soory 2006). Preliminary studies in pro-oxidant cultures of oral periosteal fibroblasts and well characterized osteoblasts demonstrated that co-enzyme Q10, phytoestrogens and the antioxidant Pycnogenol derived from pine bark, attenuated oxidative stress induced by nicotine in this model (Figuero-Ruiz et al 2006); indicating a possible role for these antioxidants in the adjunctive therapy of inflammatory diseases characterized by a pro-oxidant profile.

An uncontrolled immune response could have a synergistic effect in periodontal patients with co-existing DM (Nassar et al 2007). Effective treatment of periodontitis could improve diabetic parameters such as glycated haemoglobin (Grossi and Genco 1998). Hyperglycaemia induces oxidative stress via protein kinase-dependent activation of enzymes that catalyse the generation of reactive oxygen species from PMNs in diabetic patients with a direct bearing on periodontitis in uncontrolled diabetics (Karima et al 2005). Fundamental mechanisms associated with an over-exuberant host response are synergized in diabetic and pre-diabetic obese subjects prone to severe periodontal disease (Nishimura et al 2007).

5.3 Role of leptin in periodontal and cardiometabolic diseases

An association between periodontal disease severity and serum and gingival crevicular fluid leptin levels is well documented (Karthekayan et al 2007a,b; Bozkurt et al 2006). There is less information on the effects of periodontal treatment on serum leptin levels. Adipose tissue cells secrete over 50 bioactive substances including TNF-α and IL-6 collectively known as adipokines (Ritchie 2007; Saxlin et al 2008). Obese individuals have raised levels of circulating TNF-α and IL-6 compared with those of normal weight, with some reduction in cytokine levels on weight reduction (Ziccardi et al 2002).

There is documented evidence of a significant association between periodontitis and dyslipidaemia and that metabolic syndrome increases the risk for periodontitis; suggesting that subjects exhibiting components of metabolic syndrome should be encouraged to undergo regular periodontal examination. There are several mechanisms whereby adipose tissue mass and secretion of adipokines including leptin affect the host response. Leptin levels correlate with increasing periodontal pocket probing depths. Visceral adipose tissue in particular is an important organ that secretes several bioactive substances known as adipocytokines, including TNF-α, which contributes to periodontal disease progression. Anxiety states could correlate with visceral fat and its association with periodontal disease.

A few reports have proposed several mechanisms by which obesity can directly affect periodontal tissue. Obesity affects host immunity (Marti et al 2001), and the relationship between adipose tissue and the immune system is believed to be related to the secretion of numerous adipokines, including leptin, amounts of which correlate with fat mass (Caspar-Bauguil et al 2006). It has been demonstrated that human leptin is present within healthy and marginally inflamed gingiva, and that it could be released coincident with vascular

expansion. Gingivae, in addition to adipose tissue may be a source of circulating leptin (Johnson & Serio 2001). Recent studies have indicated that adipose tissue, especially visceral adipose tissue, is an important organ that secretes several bioactive substances known as adipocytokines, including tumor necrosis factor-α, which may enhance periodontal destruction (Saito & Shimazaki 2007).

The relationship between body mass index and events leading to risk of CHD is made complex by several factors; some of which include potential confounding factors such as smoking, medication and weight loss due to prevalent disease. The impact of body mass index on CHD is attenuated when mediators of this risk such as diabetes, hypertension and hyperlipidaemia are accounted for. It is relevant that markers of inflammation may differentiate between fatal and non-fatal events, being more strongly associated with fatal events (Logue et al 2011). The cardiovascular disease markers of inflammation, CRP and IL-6 are more significantly linked with fatal than non-fatal events (Sattar et al 2009), CRP being a weaker link than IL-6. If inflammation poses a greater risk of cardiovascular mortality, it would apply to adiposity as a source and mediator of inflammatory markers (Logue et al 2011) with important implications for treatment targets which would also apply to periodontal disease control. In addition to severity there could be subtle differences in the mechanisms involved. Treatment outcome with weight loss interventions would be a relevant area for investigation. The biological effect of obesity as a nidus of inflammation is an important one, likely to affect its role as a cardiovascular risk factor. In the context of adipose tissue functioning as an endocrine organ and releasing pro-inflammatory cytokines (Hotamisligil & Erbay 2008), obesity may be regarded as a low-grade inflammatory state (Welsh et al 2010; Cartier et al 2008).

The effects of periodontal treatment on serum levels of leptin and other cytokines adiponectin, TNF-α, IL-6 and CRP have been investigated in patients with chronic periodontitis before and after non-surgical periodontal treatment (Shimada et al 2010). The possible role of periodontal disease in producing serum leptin was investigated by determining serum leptin levels in patients with chronic periodontitis and correlated with other inflammatory markers for comparison with serum leptin levels following periodontal treatment. Serum leptin was associated with mean probing depth, clinical attachment level, alveolar bone loss and body mass index, with significant correlations between serum leptin, IL-6 and CRP levels. There were significant differences in serum leptin, IL-6 and CRP levels between healthy and chronic periodontitis patients. Non-surgical periodontal treatment was effective in reducing serum leptin, IL-6 and CRP with significant decreases in their serum levels. The efficacy of priodontal treatment in reducing these parameters is suggestive of common mediators in the progression of periodontal disease and metabolic syndrome, providing an effective therapeutic target.

Other workers have also reported that serum levels of hsCRP and IL-6 are significantly higher in periodontitis patients with decreased levels following treatment (Yamazaki et al 2005; Nakajima et al. 2010). However there was no significant association between TNF-α levels and periodontitis. An association between serum TNF-α, IL-l-6, body weight and periodontitis has been reported (Saxlin et al 2008). They suggest that IL-6 rather than TNF-α, correlated with periodontal probing depth, BMI and periodontal disease progression. The lack of significant change in serum TNF-α levels in periodontitis patients after non-surgical periodontal treatment has been reported (Ikezawa-Suzuki et al 2008), although high levels are detected in GCF or gingival tissue of periodontitis patients. It would appear that IL-6 shows clearer associations between periodontitis and systemic disease. In addition to IL-6,

IL-1 and LPS, also act as pro-inflammatory stimuli in regulating mRNA expression and circulating levels of leptin.

Leptin is also responsible for directly stimulating the production of cytokines such as IL-6 which in turn could influence the synthesis of CRP. Human CRP could inhibit receptor binding of leptin, blocking cell signalling activities; physiological concentrations of leptin stimulate CRP expression in human hepatocytes in a dose-dependent manner. This is a potential mechanism for leptin resistance whereby CRP in the circulation binds to leptin and alters its physiological functions (Chen et al 2006). It is uncertain whether changes in these cytokines reflect a common underlying cause such as obesity. A raised level of leptin during periodontal inflammation amongst other infectious / inflammatory conditions is suggestive of its role in immunolgically mediated host responses.

Leptin is also involved in modulating bone homeostasis. It stimulates bone formation directly via differentiation and proliferation of osteoblasts. It also enhances the lifespan of osteoblasts by preventing apoptosis (Gordeladze et al 2002). Leptin is implicated in bone modulatory activities in addition to local inflammation in the periodontium. Raised serum leptin levels are a risk factor for cardiovascular disease (Parhami et al 2001; Yamagishi et al 2001). Increased levels of serum leptin seen during the progression of periodontal disease, are suggestive of the influence of progressive periodontitis on cardiovascular disease. Larger studies are required to establish the connection between periodontitis and metabolic syndrome mediated by leptin.

6. Immune markers common to periodontal and cardiometabolic diseases

The effect of periodontal therapy on gene expression of peripheral blood monocytes has been investigated (Papapanou et al 2007). The time scale was 1 week before treatment, at initiation of treatment and post-treatment at 6 and 10 weeks. The periodontal status was established at baseline and subgingival plaque samples were obtained. Periodontal treatment was completed within 6 weeks. Expression profiles of monocyte RNA were determined within the stipulated time frame. Treatment resulted in improved periodontal status and reduced numbers of pathogens. About a third of patients showed significant changes in gene expression of relevance to cell signalling, apoptosis and innate immunity, consistent with a systemic anti-inflammatory effect. These responses could have a positive impact on periodontal patients presenting with cardiometabolic diseases.

There is an association between premature atherosclerosis and rheumatoid arthritis. The concept that elevated levels of inflammatory markers such as IL-6, IL-1α, TNF-α, E-selectin, ICAM-1, MMP-9 and VCAM-1 identified in atherosclerosis, are associated with the severity of coronary atherosclerosis in patients with RA, was investigated (Rho et al 2009). Levels of inflammatory mediators, clinical variables and coronary artery calcification were measured in patients with RA and in control subjects. Most of the above markers were significantly elevated in patients with RA when compared with controls; and a significant association between concentrations of IL-6 and TNF-α with greater amounts of coronary calcium. These effects were distinctly different from those of controls. It was concluded that TNF-α and IL-6 are significantly associated with the severity of sub-clinical atherosclerosis in patients with RA.

The emergence of periodontal medicine has increased interest in defining the behaviour of peripheral blood cells in periodontitis subjects in comparison with a healthy group. *E. coli* LPS-stimulated peripheral blood monocytes (PBMC) from subjects with periodontitis

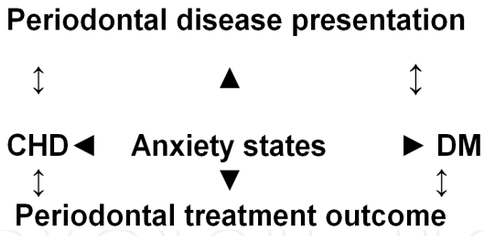
present a different pattern of cytokine release when compared to PBMC from healthy subjects, with significantly greater levels of TNF-α and IL-6 released by PBMC isolated from periodontitis subjects (Goncalves et al 2010). This phenomenon could have implications locally, in periodontitis as well as in systemic diseases, in response to circulating levels of LPS from periodontal pathogens.

Periodontopathic bacteria have been detected in 52% of atherosclerotic specimens. Cytomegalovirus (CMV) and / or *Chlamidophila pneumoniae* were detected in 4% of specimens (Chen et al 2008). After adjusting for age, gender, diabetes and smoking, periodontitis increased the risk of peripheral arterial disease by 5-fold. There were preliminary indications that periodontitis was associated with increased serum IL-6 and TNF-α concentrations which further reinforces a systemic link.

7. Conclusions

Psychosomatic pathways in the progression of periodontal and systemic diseases may not have received serious consideration. However, a sound understanding of psychosocial determinants have important implications on the host response to antigens and disease mechanisms instrumental in their progression. These concepts have far-reaching consequences in improving the efficacy of diagnoses and treatment interventions for periodontal and systemic diseases.

The schematic diagram below demonstrates that anxiety states could contribute to diseases with psychosomatic implications such as coronary heart disease (CHD), diabetes mellitus (DM) and periodontal disease. Progression of periodontal disease and its response to treatment could influence the progression of cardiometabolic disorders in a bi-directional manner. These pathways and their ramifications provide tremendous potential for future work, which is likely to clarify increasing interest in the relevance of these connections.



Comprehensive documentation of biological and physiological mechanisms by which psychosocial stress contributes to periodontal destruction provides biological rationale for this relationship. Psychosocial implications of cardiometabolic diseases addressed, converge on an inflammatory nidus as the driving force of disease progression, providing treatment options which attenuate the focus of inflammation. A relevant profile of inflammatory markers discussed provides common ground for targeting prognosis and therapeutic outcome in periodontal and cardiometabolic diseases with psychosomatic determinants, in a bi-directional manner.

Effects of treatment of periodontal disease show promising pointers towards reducing potential systemic inflammatory loading by reducing the levels of inflammatory mediators implicated in its pathogenesis. Considering the systemic impact of periodontal inflammation, effective periodontal treatment could enhance treatment outcome of

cardiometabolic co-morbidities in periodontal patients. A composite profile of inflammatory agents is likely to be more useful than individual agents in determining periodontal treatment outcome and its systemic implications. The unique role of periodontitis as a potential core nucleus of inflammation with systemic implications as discussed and extraordinary potential for treatment outcome have global implications. This has received universal documentation in the literature, underscoring the importance of early detection and intervention. Genetic and environmental predisposition could account for some of the diversity observed, in disease presentation and treatment responses.

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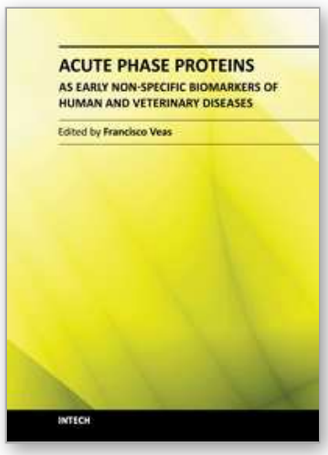

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The two volumes of Acute Phase Proteins book consist of chapters that give a large panel of fundamental and applied knowledge on one of the major elements of the inflammatory process during the acute phase response, i.e., the acute phase proteins expression and functions that regulate homeostasis. We have organized this book in two volumes - the first volume, mainly containing chapters on structure, biology and functions of APP, the second volume discussing different uses of APP as diagnostic tools in human and veterinary medicine.

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