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Review Article

C- REACTIVE PROTEIN IN VARIOUS DISEASE CONDITION – AN OVERVIEW

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ABSTRACT

C-reactive protein (CRP) was discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the C polysaccharide of pneumococcus. Initially it was thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer however discovery of hepatic synthesis demonstrated that it is a native protein. It is synthesized by the liver in response to factors released by fat cells adipocytes. It is a member of the pentraxin family of proteins. In the body, CRP plays the important role of interacting with the complement system an immunologic defense mechanism. The complement system is a group of proteins that move freely through bloodstream. The proteins work with immune system and play a role in the development of inflammation. In this review we mainly high lightens on the association of CRP with various disease conditions like, hypertension, atherosclerosis, peripheral vascular disease, diabetes, metabolic syndrome and menopause in women.

Key words: C-reactive protein, CRP, cardiovascular disease, diabetes, menopause.

INTRODUCTION

C-reactive protein (CRP) and the acute phase response were first discovered in 1930, as precipitation was observed with addition of pneumococcal C-polysaccharide to serum of a patient with acute pneumonia. This reactive material was also detected by these investigators in serum of patients with acute rheumatic fever, bacterial endocarditis, and staphylococcal osteomyelitis[1].

This reactive substance was identified with CRP by Lofstrom in 1944[2]. CRP estimations were widely carried out for the next 30 years in clinical medicine. Their assay methods were relatively insensitive and semi-quantitative[3]. CRP assays gradually fell out of common use because of positive results being non-specific response to tissue injury. In recent years, evidence has accumulated that CRP levels predict myocardial infarction, stroke, and vascular death in a variety of clinical settings[4–8].

CRP also has predictive value in chronic phase after myocardial infarction[9–10]. There is increasing evidence that CRP is not merely an important and unique risk marker, but also has a role in the pathogenesis of inflammation and atherosclerosis[11–13].

CRP is an acute phase reactant, a marker of inflammation with a half-life of 19 h. CRP has a normal range of < 2 mg/L in populations without evidence of acute illness; with illnesses such as rheumatoid arthritis or sepsis, and concentrations can increase up to 300 mg/L. In vitro studies shown that aggregated CRP binds to low and very-low density lipoprotein, which in turn activates complement, stimulates tissues factor production by macrophages, and thus starts coagulation. This may play an important role in the connection between CVD and CRP[14].

C- reactive protein **(**CRP) is an acute-phase reactant and belongs to the pentraxin family of ligand-binding and calcium-dependent plasma proteins. CRP levels increases in a variety of infections, immuno-inflammatory diseases, trauma, and malignancies. CRP levels may be increase up to 50 to 100 mg/L in acute infections, whereas levels generally remain below 10 mg/L in persons with significant atherosclerosis[15]. High CRP level in an asymptomatic person is relevant when assessing cardiovascular risk. Plasma half-life of CRP remains constant under all physiologic and pathologic conditions. These levels rapidly rise and fall after introduction and cessation of stimulus, respectively.

Synthesis of CRP occurs in hepatocytes and regulated primarily by interleukin-1, interleukin-6, and tumor necrosis factor-α (TNF-α). These proinflammatory cytokines are related closely to insulin glucose metabolism and insulin resistance. It is speculated that low-grade inflammation within the arteries and atherosclerotic plaques can raise CRP levels. However, it may occur due to clinically in apparent infection (e.g., *Helicobacter pylori*). Further, infectious agents implicated in the causation of coronary heart disease (*Chlamydia pneumoniae, Helicobacter pylori*) also increases CRP levels. It also may have a direct role in the pathogenesis of atherosclerosis and vascular inflammation[17,18].

CRP is even more relevant in Asian Indians who are at high risk for the development of insulin resistance, type 2 diabetes mellitus, and coronary heart disease[19-22].

Many risk factors have been reported higher in Asian Indians than in Europeans including insulin resistance, abdominal adiposity, atherogenic dyslipidemia, procoagulant factors, endothelial dysfunction, and hyperhomocysteinemia and subclinical inflammation is a recent addition to this long list[23].

CRP concentration does not have any diurnal variations and is unaffected by eating; hence, it can be estimated in a non-fasting blood sample.

SYNTHESIS AND METABOLISM

CRP is synthesized and secreted mainly by hepatocytes in response to cytokines such as interleukin-6. Induction of CRP in some models requires both interleukin 6 and either interleukin-1 or TNF-α[24]. CRP is primarily derived via IL 6- dependent hepatic biosynthesis. Glucocorticoids enhance the stimulatory effects of cytokines on the production of acute phase proteins[25]. Insulin, on the other hand, decreases their effects on the production of some acute phase proteins[26]. Efficiency of secretion of CRP is greatly increased during acute-phase response[27]. During an acute phase response the rate of secretion into the plasma may be relatively constant and the concentration achieved is dependent upon the duration of stimulation and resulting response by the liver[28]. Newly synthesized CRP is rapidly secreted by liver cells and hence difficult to show within the cytoplasm. Colchicine blocks secretion but not synthesis and would increase the accumulation of CRP intracellularly[29]. Both production and clearance of CRP is very rapid. Endotoxin treatment doubles the levels of CRP within 6–8 hours and half disappearance time is 11–15 hours.

CONDITIONS OR DISEASE STATES WHERE C-REACTIVE PROTEIN IS ELEVATED[30]

A. Acute inflammation:

- Bacterial infection
- Pneumococcal pneumonia
- Acute rheumatic fever
- Bacterial endocarditis

- Staphylococcal osteomyelitis

B. Chronic inflammation:

- Systemic lupus erythematosis
- Rheumatic arthritis
- Reiter's syndrome, psoriatic arthriopathy, arthritis following jejuno-ileal bypass
- Polyarteritis nodosa, disseminated
- systemic vasculitis, cutaneous vasculitis
- Polymyalgia rheumatica
- Crohn's disease
- Ulcerative colitis
- Dermomyositis
- Osteoarthritis
- Neoplastic diseases
- Smokers
- Obesity
- Diabetes

C. Tissue injury:

- Tissue injury and surgery
- Acute myocardial ischemia

CRP AND CARDIOVASCULAR DISEASES

In January 2003, a joint panel of experts from the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC) released a statement acknowledging that testing for CRP is useful in determining a patient's risk for cardiovascular disease. A growing body of scientific data links CRP with cardiovascular events. Studies indicate that patients with the highest levels of CRP have about twice the risk as those with the lowest levels.

High plasma concentration of CRP was associated with a 2-fold increase in risk of stroke, a 3-fold increase in risk of myocardial infarction (MI), and a 4-fold increase in risk of developing peripheral vascular disease. Hypertension showed increased levels of several inflammatory markers, including soluble leukocyte adhesion molecules. Chemotactic and proinflammatory cytokines, specific growth factors, heat shock proteins and $CD_{40}L$. CRP concentrations among hypertension might be explained by a clustering of common positive CRP covariates (i.e. age, female sex, and increased body mass index and lipid concentrations) among hypertensive patients. The association between elevated CRP levels and high blood pressure may have three different pathophysiological explanations[31].

The clinical relevance of CRP determination in subjects without clinically overt ischemic heart disease is still controversial. However, in a recent report of the Reykjavik Study, Danesh et al. confirmed CRP is an independent predictor of coronary heart disease, but the CRP-associated odds ratio was lower than that of established cardiovascular risk factors such as systolic blood pressure, smoking, and total cholesterol[32].

C-REACTIVE PROTEIN AND HYPERTENSION

PATHOPHYSIOLOGIC IMPLICATIONS

In a number of cross-sectional studies, patients with essential hypertension showed increased levels of several inflammatory markers, including soluble leukocyte adhesion molecules chemotactic and proinflammatory cytokines specific growth factors heat shock proteins and CD40L[33,34]. Some cross-sectional studies reported greater plasma CRP concentrations in treated or untreated patients with hypertension than in normotensive individuals. However, the effects of current or previous antihypertensive treatment and of hypertension duration could not be excluded in those studies. Moreover, in some of these studies, greater plasma CRP concentrations among patients with hypertension might be explained by a clustering of common positive CRP covariates (i.e. age, female sex, increased body mass index and lipid concentrations) among hypertensive patients[35,36].

The association between elevated CRP levels and high blood pressure may have three different pathophysiologic explanations (Fig. 1). First, causation may be involved, and indeed several studies hypothesise that CRP may induce a decrease in endothelium-dependent relaxation, a potential risk factor for hypertension (see below). Reverse causation might also be implicated, whereby high blood pressure may induce inflammation and raise CRP levels. On the other hand, the association could be explained by confounding, because CRP and high blood pressure share several risk factors such as lower sociodemographic position, lack of physical activity, smoking, and abdominal obesity[37,38].

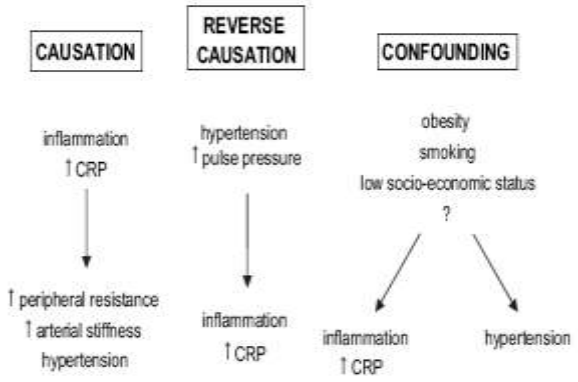

Figure -1: It Shown Hypothetical Causative Pathways Linking Elevated C-Reactive Protein Levels And Hypertension.

CAUSATIVE CONNECTION

Several studies suggest that; CRP may have negative effects on vascular function and structure, and recent data have clearly documented that CRP is produced not only by the liver, but also in human atheroma by vascular smooth muscle cells and endothelial cells. Higher levels of CRP may increase blood pressure through a variety of biological effects in endothelial cells, which ultimately result in vasoconstriction and increased production of endothelin-1. The putative proatherogenic and hypertensive effects of CRP might also be mediated by upregulation of angiotensin type 1 receptor expression .Despite the documented effects of CRP on the vessel wall, its role in vascular biology remains elusive. Indeed, some data suggest that CRP might inhibit neutrophil adhesion and platelet aggregation. These contradictory data can be in part reconciled when considering that CRP could dissociate into individual subunits during inflammation[39].

Effects of C-reactive protein on vascular endothelium

- Prostacyclin
- Plasminogen activator inhibitor-1
- Tissue plasminogen activator
- Cell adhesion molecules, E-selectin, monocyte chemotactic protein-1
- Endothelial nitric oxide synthase
- Matrix metalloproteinase-1, -10
- Endothelin-1
- Monocyte recruitment
- Endothelial progenitor cell survival, differentiation, and function

REVERSE CAUSALITY

Hypertension may accelerate the atherosclerotic process through inflammatory mechanisms mediated by the vasoactive peptides angiotensin II and endothelin- 1. A number of mechanisms may account for the proinflammatory effects of angiotensin II. Angiotensin II is primarily involved in the inflammatory process by modulating proinflammatory transcription factors such as NF-kB, and by inducing the release of cytokines. Angiotensin II is also responsible for the activation of nicotinamide adeninedinucleotide (phosphate) (NADPH) oxidase in endothelial cells and in vascular smooth muscle cells. NADPH oxidase is the major source of vascular reactive oxygen species, which lead to endothelial dysfunction, endothelial growth, inflammation, and upregulation of endothelin-1. The renal protection afforded by inhibitors of the renineangiotensinealdosterone system appears to be at least in part due to inhibition of tissue macrophage infiltration. Moreover, pharmacological inhibition of the renineangiotensinealdosterone system results in reduced endothelial dysfunction, oxidative stress, inflammation, and plasminogen activator inhibitor-1 concentration. Endothelin- 1 is an important mediator of vascular inflammation in its own, via activation of NF-kB and NAD(P)H oxidase. Cyclic strain has been shown to increase adhesion molecule expression by endothelial cells, to upregulate endothelial cell secretion of proinflammatory cytokines, which result in enhanced monocyte adhesion to the endothelium, and to increase oxidative stress in endothelial Cells[40, 43].

CRP AND ATHEROSCLEROSIS

CRP could induce atherosclerosis in various ways: a) oxygen radicals, and b) adhesion molecules.

a) Oxygen Radicals

CRP activates complement platelets and induces expression of cytokines. Activated complement platelet-activating factor and cytokines stimulate leukocytes to release oxygen radicals. CRP also enhances the generation of oxygen free radicals by monocytes and neutrophils directly. Oxygen radicals have been implicated in the pathophysiology of atherosclerosis. The oxidative hypothesis of atherosclerosis depends upon the oxygen radicals[44,45].

b) Adhesion Molecules

Cell adhesion molecules are involved in atherogenesis. CRP induces expression of adhesion molecules in the endothelial cells and MCP-1 Oxygen radicals generated by CRP could also increase the expression of adhesion molecules. Expression of adhesion molecules by arterial endothelial cells is modulated by free radicals and oxidative stress and suppressed by antioxidants[46,47].

CRP AND PERIPHERAL VASCULAR DISEASE

Total cholesterol/HDL-C ratio and CRP were the strongest independent predictors of development of peripheral arterial disease of the two inflammatory variables (CRP and fibrinogen). TC/HDL-C ratio and CRP were equally effective predictors. CRP has been related both cross-sectionally and prospectively to peripheral arterial disease[48,49]. CRP and atherosclerosis measured at various sites (carotid, aortic iliac and lower extremity). However, there are reports that show a strong association between CRP and progression of carotid atherosclerosis. Recently it has been reported that CRP predicts progression of atherosclerosis measured at various sites in the arterial tree[50].

CRP AND DIABETES

Type II diabetes has higher risk for all vascular diseases, including ischemic heart disease, cerebrovascular disease, and peripheral vascular disease. These macrovascular complications usually result from atherosclerosis. Cardiovascular complications are the major cause of mortality and morbidity individuals worldwide affected by type 2 DM[51].

Hyperglycaemia is known to stimulate the release of the inflammatory cytokines TNF- and IL-6 from various cell types. Hyperglycaemia can result in the induction and secretion of acute-phase reactants by adipocytes. Prolonged exposure to hyperglycemia is now recognized as the primary causal factor in the pathogenesis of diabetic complications including atherosclerosis in monocytes, chronic hyperglycemia causes a dramatic increase in the release of cytokines. Hyperglycemia directly examined the association between CRP and fasting insulin, fasting glucose and insulin resistance[52].

Diabetes itself is also associated with defective endothelium-dependent relaxation, impaired nitric oxide (NO) generation, and enhanced NO destruction. Endothelial dysfunction is a common feature in diabetic patients and may contribute to cardiovascular morbidity. Mechanisms of diabetes-induced endothelial dysfunction include the production of prostanoid vasoconstrictors and the increased oxidative degradation of NO. Deficiency of NO increases vascular resistance and promotes atherogenesis. In addition to its increased oxidative degradation, another possible mechanism for NO deficiency and cardiovascular morbidity is reduced NO synthesis caused by asymmetric dimethylarginine (ADMA). ADMA is an endogenous competitive inhibitor of NO synthase (NOS). This modified amino acid is derived from proteins that have been posttranslationally methylated and subsequently hydrolyzed the enzyme dimethylarginine dimethylaminohydrolase (DDAH) accounts for most of the clearance of ADMA.DDAH metabolizes ADMA to L-citrulline and dimethylamine. ADMA is elevated to a level that can significantly inhibit NOS activity in individuals with hypercholesterolemia, hypertension, hyperhomocysinemia, tobacco exposure, and hyperglycemia[53].

Diabetic individuals have higher concentrations of CRP and it closely related to adiposity. The increased level of serum CRP in obese individuals is due to increased secretion of interleukin-6 and tumor necrosis factor in adipocytes, which regulate CRP production in hepatocytes and induce a chronic inflammatory state.

Elevated levels of CRP and plasminogen-activator inhibitor (PAI) have been demonstrated to predict the incidence of type 2 diabetes. Abdominal obesity and the subsequent secretion of pro-inflammatory cytokines and acute phase reactants may contribute to the relationship between chronic inflammation and type 2 diabetes. Adipocytes (fat cells) cells that secrete IL-6 and the amount of IL-6 produced by adipocytes are proportional to the amount of fat cell mass[54].

CRP AND METABOLIC SYNDROME

Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III), inflammation, as assessed by C-reactive protein (CRP), is emerging as a predictor of cardiovascular disease (CVD), and it may be an important precursor of the metabolic syndrome (MetS). Definition of the metabolic syndrome that includes the presence of at least 3 of the following characteristics: abdominal obesity, elevated triglycerides, reduced levels of HDL cholesterol, high blood pressure, and high fasting glucose. However, all of these parameters are associated with elevated levels of C-reactive protein. CRP levels also correlate with several other components of the metabolic syndrome such as fasting insulin, microalbuminuria, and impaired fibrinolysis that are not easily evaluated in usual clinical practice[55].

Obesity could be the proinflammatory cytokines produced by adipose tissue such as tumor necrosis factor and interleukin-6. These cytokines can influence insulin resistance and glucose uptake, promote hepatic fatty acid synthesis, and increase hepatic CRP production. Inflammation, including CRP, was more strongly related to insulin resistance and/or the NCEP MetS[56].

Insulin resistance may promote atherosclerosis and predispose to the development of the metabolic syndrome and diabetes by several mechanisms. IL-6 may interfere with insulin signalling through the induction of proteins that bind to the insulin receptor, and it appears to down-regulate corticosteroid-binding globulin, which may lead to increased free cortisol concentrations, insulin resistance and other manifestations of the metabolic syndrome. In addition, IL-6 stimulates the secretion of major pro-inflammatory cytokines. TNF-

α decreases insulin-mediated glucose uptake and impairs endothelial function. Pro-inflammatory cytokines, and possibly CRP, may also directly promote atherosclerosis and thrombosis by the induction of nuclear factor-κB and the release of adhesion molecules and plasminogen activator inhibitor-1[57].

CRP levels and Plasminogen activator inhibitor-1 (PAI-1), a marker of atherothrombosis, are increased in the metabolic syndrome. Furthermore, both PAI-1 and CRP levels seem to be elevated and cosegregate with the different features of the metabolic syndrome. PAI-1 is a key regulator of fibrinolysis by inhibiting tissue plasminogen activator (tPA). Decreased fibrinolysis, primarily attributable to increased PAI-1 activity, has been demonstrated in with coronary artery disease (CAD)[58].

Furthermore, higher CRP levels were associated with an increased risk of MetS, and this association was independent of lifestyle factors, education level, family history of chronic diseases, and body mass index (BMI)[59].

CRP AND MENOPAUSAL WOMEN

In women, especially after the menopause transition, has been linked with a number of metabolic complications, such as dyslipidemia, insulin resistance, hypertension, and an increased risk of coronary heart disease. It is not known whether aerobic fitness, body composition, body fat distribution, or markers of inflammation are associated with the number of MetS components in postmenopausal women[60].

CRP was related to age-adjusted measures of body composition (as a surrogate of body fat) and physical fitness. The strongest association was seen for waist circumference and BMI.

After menopause higher levels of E1 (oestrone), E2 (oestradiol), FEI (free oestradiol index), T (testosterone), FAI (free androgen index), and lower levels of SHBG (sex hormone binding globulin) were independently associated with higher levels of CRP, even after adjustment for traditional risk factors and markers of body composition or physical activity. Fat tissue expresses aromatase, and conversion of testosterone to oestrogen by aromatase is one of the main sources for endogenous oestrogen in postmenopausal women. The evaluation of direct effects of endogenous oestrogen levels on CRP is complicated because adipose tissue produces inflammatory mediators that increase CRP production in the liver.

Increase in CRP level after menopause is the product of several concurring events. First, ageing itself was a strong determinant of increase in CRP as were traditional risk markers such as HDL cholesterol, alcohol intake and pulse pressure. Secondly, sex hormones such as E1, E2, FEI, T and FAI were also strongly positively associated with age-adjusted CRP levels whereas SHBG showed a strong negative association. Additional traditional risk factors accounted for a modest attenuation of this association, but the relationship remained highly statistically significant. Thirdly, when the level of adjustment was expanded to markers of body build, the associations were again modestly attenuated but remained significant. This observation suggests that a considerable part of the increased CRP after menopause is explained by ageing, the alteration in the sex hormone profile and changes in body composition[61].

Additionally, effects of hormone therapy (HT) on CRP levels should be evaluated in selecting the appropriate treatment. Route of administration may be of consequence: elevated levels of CRP have been associated with oral but not with transdermal HT. Interestingly, the American Society for Reproductive Medicine HT guidelines suggest that route of HT administration may have an effect on potential risk[62].

Healthy postmenopausal women, found four markers of inflammation as CRP, serum amyloid A, interleukin-6, and intercellular adhesion molecule type 1 (sICAM-1) were significant predictors of the risk of future cardiovascular events. Obesity positively associated with plasma CRP, and adipose tissue has directly modulating CRP levels. Losses of fat mass in obese postmenopausal women were associated with proportional reductions in plasma CRP levels[63].

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