“A STUDY OF CORRELATION OF C – REACTIVE PROTEIN WITH CAROTID ATHEROSCLEROSIS IN DYSLIPIDEMIC PATIENTS”

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"A STUDY OF CORRELATION OF CRP LEVELS WITH CAROTID ATHEROSCLEROTIC PLAQUES IN DYSLIPIDEMIC PATIENTS"

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CERTIFICATE

This is to certify that this dissertation**. "A study of correlation of CRP levels with carotid atherosclerotic plaques in dyslipidemic patients"** is a bonafide work done by Dr.Denesh Narasimhan in the Department of Medicine ***P.S.G. Institute of Medical Sciences and Research,*** Coimbatore under my supervision and guidance.

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INTRODUCTION

Atherosclerosis is a inflammatory disease affecting the large and medium sized blood vessels.Serum levels of C-reactive protein, a major acute phase protein represents a clinical marker of inflammation.

Recent data has revealed that CRP has been positively been associated with atherosclerosis. CRP has been found to be positively associated with acute myocardial infarction and with sudden deaths in patients with stable and unstable angina.[1]Baseline levels of CRP in healthy subjects have been shown to predict development of symptomatic peripheral vascular disease. Coronary artery disease or both.[2]

An association between CRP and number of stenosed coronary vessels has been documented in coronary atherosclerosis.[3]In relation to carotid atherosclerosis, two studies have shown the relation between CRP levels and carotid plaques.In one study there was a significant relation between CRP and early non-stenotic atherosclerosis.[4]In anotherstudy there was correlation between CRP levels and prescence of atherosclerosis in the coronary, extracranial cerebrovascular and in the vasculature of the extremities.[5] Patients without any of the conventional risk factors[smoking,diabetesmellitus,hypertension,dyslipidemia] for atherosclerosis are considered to be at low risk.

As demonstrated in one study CRP is of special value only in patients in whom at least one of the four major risk factors are present.CRP is a proven risk factor in hypercholesteremic patients.[6]Hence this study was focused on a group of dyslipidemic\ patients.

AIM OF THE STUDY

The aim of the study is to determine whether CRP concentrations correlated with the prescence of carotid atherosclerotic plaques in a subset of dyslipidemic patients.

LITERATURE REVIEW

Atherosclerosis is an inflammatory disease. Because high plasma concentrations of cholesterol, in particular those of low-density lipoprotein (LDL) cholesterol, are one of the principal risk factors for atherosclerosis[7] the process of atherogenesis has been considered by many to consist largely of the accumulation of lipids within the artery wall; . In fact, the lesions of atherosclerosis represent a series of highly specific cellular and molecular responses that can best be described, in aggregate, as an inflammatory disease. The lesions of atherosclerosis occur principally in large and medium-sized elastic and muscular arteries and can lead to ischemia of the heart, brain, or extremities, resulting in infarction. They may be present throughout a person's lifetime. In fact, the earliest type of lesion, the so-called fatty streak, which is common in infants and young children, is a pure inflammatory lesion, consisting only of monocyte-derived macrophages and T lymphocytes.[8] In persons with hypercholesterolemia, the influx of these cells is preceded by the extracellular deposition of amorphous and membranous lipids..

FACTORS THAT INDUCE AND PROMOTE ATHEROGENESIS OR INFLAMMATION

Numerous pathophysiologic observations in humans and animals led to the formulation of the response-to-injury hypothesis of atherosclerosis, which initially proposed that endothelial denudation was the first step in atherosclerosis.[9] The most recent version of this hypothesis emphasizes endothelial dysfunction rather than denudation. Whichever process is at work, each characteristic lesion of atherosclerosis represents a different stage in a chronic inflammatory process in the artery; if unabated and excessive, this process will result in an advanced, complicated lesion. Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified LDL; free radicals caused by cigarette smoking, hypertension, and diabetes mellitus; genetic alterations; elevated plasma homocysteine concentrations; infectious microorganisms such as herpesviruses or *Chlamydia pneumoniae*; and combinations of these or other factors.

Regardless of the cause of endothelial dysfunction, atherosclerosis is a highly characteristic response of particular arteries. The endothelial dysfunction that results from the injury leads to compensatory responses that alter the normal homeostatic properties of the endothelium. Thus, the different forms of injury increase the adhesiveness of the endothelium with respect to leukocytes or platelets, as well as its permeability. The

injury also induces the endothelium to have procoagulant instead of anticoagulant properties and to form vasoactive molecules, cytokines, and growth factors. If the inflammatory response does not effectively neutralize or remove the offending agents, it can continue indefinitely. In doing so, the inflammatory response stimulates migration and proliferation of smooth-muscle cells that become intermixed with the area of inflammation to form an intermediate lesion. If these responses continue unabated, they can thicken the artery wall, which compensates by gradual dilation, so that up to a point, the lumen remains unaltered,[10] a phenomenon termed "remodeling." As for the inflammatory cells, granulocytes are rarely present during any phase of atherogenesis. Instead, the response is mediated by monocyte -derived macrophages and specific subtypes of T lymphocytes at every stage of the disease.

Continued inflammation results in increased numbers of macrophages and lymphocytes, which both emigrate from the blood and multiply within the lesion. Activation of these cells leads to the release of hydrolytic enzymes, cytokines, chemokines, and growth factors, which can induce further damage and eventually lead to focal necrosis.[11] Thus, cycles of accumulation of mononuclear cells, migration and proliferation of smooth-muscle cells, and formation of fibrous tissue lead to further enlargement and restructuring of the lesion, so that it becomes covered by a fibrous cap that overlies a core of lipid and

necrotic tissue — a so-called advanced, complicated lesion. At some point, the artery can no longer compensate by dilation; the lesion may then intrude into the lumen and alter the flow of blood.

HYPERCHOLESTEROLEMIA AND MODIFIED LIPIDS AND LIPOPROTEINS

Lipids, which may be modified by oxidation, glycation (in diabetes), aggregation , association with proteoglycans, or incorporation into immune complexes,[12] is a major cause of injury to the endothelium and underlying smooth muscle When LDL particles become trapped in an artery, they can undergo progressive oxidation and be internalized by macrophages by means of the scavenger receptors on the surfaces of these cells.[13] The internalization leads to the formation of lipid peroxides and facilitates the accumulation of cholesterol esters, resulting in the formation of foam cells.

The degree to which LDL is modified can vary greatly.[13] Once modified and taken up by macrophages, LDL activates the foam cells. Removal and sequestration of modified LDL are important parts of the initial, protective role of the macrophage in the inflammatory response and minimize the effects of modified LDL on endothelial and smooth-muscle cells. Antioxidants such as vitamin E can also reduce free-radical formation by modified LDL. In addition to its ability to injure these cells, modified

LDL is chemotactic for other monocytes and can up-regulate the expression of genes for macrophage colony-stimulating factor and monocyte chemotactic protein derived from endothelial cells. Thus, it may help expand the inflammatory response by stimulating the replication of monocyte-derived macrophages and the entry of new monocytes into lesions.

The inflammatory response itself can have a profound effect on lipoprotein movement within the artery. Specifically, mediators of inflammation such as tumor necrosis factor α, interleukin-1, and macrophage colony-stimulating factor increase binding of LDL to endothelium and smooth muscle and increase the transcription of the LDL-receptor gene.[14] After binding to scavenger receptors in vitro, modified LDL initiates a series of intracellular events[15] that include the induction of urokinase and inflammatory cytokines such as interleukin-1. Thus, a vicious circle of inflammation, modification of lipoproteins, and further inflammation can be maintained in the artery by the presence of these lipids.

Oxidized LDL is present in lesions of atherosclerosis in humans.[16] In animals with hypercholesterolemia, antioxidants can reduce the size of lesions, and they reduce fatty streaks in nonhuman primates. The latter observation suggests that the antioxidants have an antiinflammatory effect, perhaps by preventing the up-regulation of

adhesion molecules for monocytes. Antioxidants increase the resistance of human LDL to oxidation ex vivo[17] in proportion to the vitamin E content of the plasma. Vitamin E intake is inversely correlated with the incidence of myocardial infarction, and vitamin E supplementation reduced coronary events in a preliminary clinical trial In contrast, other antioxidants, such as beta carotene, have no benefit

.**HOMOCYSTEINE**

High plasma homocysteine concentrations were initially thought to be associated with advanced atherosclerosis on the basis of autopsy findings in patients with homozygous defects in enzymes necessary for homocysteine metabolism, such as cystathionine beta -synthase or methylenetetrahydrofolate reductase.[18] In patients with such defects, severe atherosclerosis develops in childhood, and many have their first myocardial infarction by the age of 20 years Homocysteine is toxic to endothelium[19] and is prothrombotic, and it increases collagen production and decreases the availability of nitric oxide.

Plasma homocysteine concentrations are slightly elevated in many patients who have no enzymatic defects in homocysteine metabolism. These patients have an increased risk of symptomatic atherosclerosis of the coronary, peripheral, and cerebral arteries Treatment with folic acid can return their plasma homocysteine concentrations to normal. Trials are under way to determine whether folic acid will prevent the

progression or possibly even induce the regression of atherosclerotic lesions.

HYPERTENSION

Concentrations of angiotensin II, the principal product of the renin–angiotensin system, are often elevated in patients with hypertension; angiotensin II is a potent vasoconstrictor. In addition to causing hypertension, it can contribute to atherogenesis by stimulating the growth of smooth muscle.[20] Angiotensin II binds to specific receptors on smooth muscle, resulting in the activation of phospholipase C, which can lead to increases in intracellular calcium concentrations and in smooth-muscle contraction, increased protein synthesis, and smooth-muscle hypertrophy. It also increases smooth -muscle lipoxygenase activity, which can increase inflammation and the oxidation of LDL. Hypertension also has proinflammatory actions, increasing the formation of hydrogen peroxide and free radicals such as superoxide anion and hydroxyl radicals in plasma. These substances reduce the formation of nitric oxide by the endothelium,[21] increase leukocyte adhesion and increase peripheral resistance. Thus, free-radical formation mediates some of the effects of both hypertension and hypercholesterolemia.

INFECTION

Several reports have shown a correlation between the incidence of atherosclerosis and the presence of at least two types of infectious microorganisms, herpesviruses and *C. pneumoniae*[22] Both organisms have been identified in atheromatous lesions in coronary arteries and in other organs obtained at autopsy. Increased titers of antibodies to these organisms have been used as a predictor of further adverse events in patients who have had a myocardial infarction. Nonetheless, there is no direct evidence that these organisms can cause the lesions of atherosclerosis.

Although these organisms are ubiquitous in many tissues and organs, the fact that lesions cannot be induced experimentally in animals by injection of the organisms leaves their role as etiologic agents in question. It is nevertheless possible that infection, combined with other factors, may be responsible for the genesis of the lesions of atherosclerosis in some patients.

THE NATURE OF THE INFLAMMATORY RESPONSE

Interactions among Endothelial Cells, Monocytes, and T Cells

Specific arterial sites, such as branches, bifurcations, and curvatures, cause characteristic alterations in the flow of blood, including decreased shear stress and increased turbulence.[23] At these sites,

specific molecules form on the endothelium that are responsible for the adherence, migration, and accumulation of monocytes and T cells.

Such adhesion molecules, which act as receptors for glycoconjugates and integrins present on monocytes and T cells, include several selectins, intercellular adhesion molecules, and vascular-cell adhesion molecules.[24] Molecules associated with the migration of leukocytes across the endothelium, such as platelet–endothelial-cell adhesion molecules,[25] act in conjunction with chemoattractant molecules generated by the endothelium, smooth muscle, and monocytes — such as monocyte chemotactic protein 1 osteopontin to bind to monocytes and other WBC.,

The nature of the flow — that is, whether shear stress or turbulence is high or low — appears to be important in determining whether lesions occur at these vascular sites. Changes in flow alter the expression of genes that have elements in their promoter regions that respond to shear stress. For example, the genes for intercellular adhesion molecule 1, platelet-derived growth factor B chain, and tissue factor in endothelial cells have these elements, and their expression is increased by reduced shear stress.[26]

Thus, alterations in blood flow appear to be critical in determining which arterial sites are prone to have lesions Rolling and adherence of monocytes and T cells occur at these sites as a result of the up-

regulation of adhesion molecules on both the endothelium and the leukocytes.

Chemokines may be responsible for the chemotaxis and accumulation of macrophages in fatty streaks.[27] Activation of monocytes and T cells leads to up-regulation of receptors on their surfaces, such as the mucin-like molecules that bind selectins, integrins that bind adhesion molecules of the immunoglobulin superfamily, and receptors that bind chemoattractant molecules[28] . These ligand–receptor interactions further activate mononuclear cells, induce cell proliferation, and help define and localize the inflammatory response at the sites of lesions. In genetically modified mice that are deficient in apolipoprotein E (and have hypercholesterolemia), intercellular adhesion molecule 1 is constitutively increased at lesion-prone sites.[29] In fact, it is present on the surface of the endothelium at these sites in normal mice and is increased in mice with apolipoprotein E deficiency. In contrast, vascular-cell adhesion molecule 1 is absent in normal mice but is present at the same sites as intercellular adhesion molecule 1 in mice with apolipoprotein E deficiency.

Thus, adherence of monocytes and T cells may occur after an increase in one or more of the adhesion molecules, which may act in concert with chemotactic molecules such as monocyte chemotactic protein 1, interleukin-8, or modified LDL. In mice that are completely

deficient in intercellular adhesion molecule 1, P-selectin, CD18, or combinations of these molecules, lipid feeding leads to smaller lesions of atherosclerosis.[30] Comparison of the relative roles of these molecules in inflammation in the arteries and the microvasculature may provide clues to the relative feasibility of modifying the inflammatory process at these sites, and thus of modifying therosclerosis.

METALLOPROTEINASE LIKE PROTEINS

A recently discovered class of molecules, the disintegrins, sometimes called metalloproteinase-like, disintegrin-like, cysteine-rich proteins (MDCs), has been identified in endothelium, smooth muscle, and macrophages. These transmembrane proteins, which appear to be involved in cell–cell interactions, contain a metalloproteinase sequence in their extracellular segment that permits them to activate molecules such as tumor necrosis factor . They are not found in normal arteries, but one of them, MDC15, is present in lesions of atherosclerosis. Adhesion molecules such as L-selectin can be cleaved from the surface of leukocytes by a metalloproteinase (L-selectin sheddase), which suggests that in situations of chronic inflammation it may be possible to measure the "shed" molecules, such as the different adhesion molecules, in plasma, as markers of a sustained inflammatory response.[31] Disintegrins may participate in these shedding processes. If shedding

occurs, it may be detectable in different types of inflammatory responses. Increased plasma concentrations of shed molecules might then be used to identify patients at risk for atherosclerosis or other inflammatory diseases.

MONOCYTES AND IMMUNITY

The ubiquitous monocyte, the precursor of macrophages in all tissues, is present in every phase of atherogenesis. Monocyte-derived macrophages are scavenging and antigen-presenting cells, and they secrete cytokines, chemokines, growth-regulating molecules, and metalloproteinases and other hydrolytic enzymes. The continuing entry, survival, and replication of mononuclear cells in lesions depend in part on factors such as macrophage colony-stimulating factor and granulocyte–macrophage colony-stimulating factor for monocytes and interleukin-2 for lymphocytes. Continued exposure to macrophage colony-stimulating factor permits macrophages to survive in vitro and possibly to multiply within the lesions. In contrast, inflammatory cytokines such as interferon-γ activate macrophages and under certain circumstances induce them to undergo programmed cell death (apoptosis). If this occurs in vivo, macrophages may become involved in the necrotic cores characteristic of advanced, complicated lesions.

Initially, the only cells thought to proliferate during expansion of atherosclerotic lesions were smooth-muscle cells. However, replication of

monocyte-derived macrophages and T cells is probably of equal importance.[32] The ability of macrophages to produce cytokines (such as tumor necrosis factor α, interleukin-1, and transforming growth factor ß), proteolytic enzymes (particularly metalloproteinases), and growth factors (such as platelet-derived growth factor and insulin-like growth factor I) may be critical in the role of these cells in the damage and repair that ensue as the lesions progress. Macrophagesexpress class II histocompatibility antigens such as HLA-DR that allow them to present antigens to T lymphocytes. Thus, it is not surprising that cell-mediated immune responses may be involved in atherogenesis, since both CD4 and CD8 T cells are present in the lesions at all stages of the process. T cells are activated when they bind antigen processed and presented by macrophages. T-cell activation results in the secretion of cytokines, including interferon-γ and tumor necrosis factor αand ß, that amplify the inflammatory response. Smooth-muscle cells from the lesions also have class II HLA molecules on their surfaces, presumably induced by interferon-γ, and can also present antigens to T cells. One possible antigen may be oxidized LDL, which can be produced by macrophages. Heat-shock protein 60 may also contribute to autoimmunity. This and other heat-shock proteins perform several functions, including the assembly, intracellular transport, and breakdown of proteins and the prevention of protein denaturation. These proteins may be elevated on endothelial cells and participate in immune responses.

An immunoregulatory molecule, CD40 ligand, can be expressed by macrophages, T cells, endothelium, and smooth muscle in atherosclerotic lesions in vivo, and its receptor, CD40, is expressed on the same cells. Both are up-regulated in lesions of atherosclerosis, providing further evidence of immune activation in the lesions. Furthermore, CD40 ligand induces the release of interleukin-1ß by vascular cells, potentially enhancing the inflammatory response. Inhibition of CD40 with blocking antibodies reduces lesion formation in apolipoprotein E–deficient mice.

PLATELETS

Platelet adhesion and mural thrombosis are ubiquitous in the initiation and generation of the lesions of atherosclerosis in animals and humans. Platelets can adhere to dysfunctional endothelium, exposed collagen, and macrophages. When activated, platelets release their granules, which contain cytokines and growth factors that, together with thrombin, may contribute to the migration and proliferation of smooth-muscle cells and monocytes.[33] Activation of platelets leads to the formation of free arachidonic acid, which can be transformed into prostaglandins such as thromboxane A_2, one of the most potent vasoconstricting and platelet-aggregating substances known, or into leukotrienes, which can amplify the inflammatory response.

Plaque rupture and thrombosis are notable complications of advanced lesions that lead to unstable coronary syndromes or myocardial infarction.[35] Platelets are important in maintaining vascular integrity in the absence of injury and protecting against spontaneous hemorrhage. Activated platelets can accumulate on the walls of arteries and recruit additional platelets into an expanding thrombus. An important component of the platelets is the glycoprotein IIb/IIIa receptor, which belongs to the integrin superfamily of adhesion-molecule receptors and appears on the surface of platelets during platelet activation and thrombus formation. These receptors serve an important hemostatic function, and antagonists to them prevent thrombus formation in patients who have had a myocardial infarction.

ATHEROSCLEROSIS IN RELATION TO OTHER CHRONIC INFLAMMATORY DISEASES

The cellular interactions in atherogenesis are fundamentally no different from those in chronic inflammatory–fibroproliferative diseases such as cirrhosis, rheumatoid arthritis, glomerulosclerosis, pulmonary fibrosis, and chronic pancreatitis.. Thus, the cellular responses in the arteries (atherosclerosis), liver (cirrhosis), joints (rheumatoid arthritis), kidneys (glomerulosclerosis), lungs (pulmonary fibrosis), and pancreas (pancreatitis) are similar yet are characteristic of each tissue or organ.

INFLAMMATORY RESPONSE

Granulocytes are rare in atherosclerosis,they are present only in rheumatoid arthritis and pulmonary fibrosis. In the case of arthritis, although the early response begins with granulocytes, they are found primarily within the joint cavity. Macrophages and lymphocytes predominate in the synovium, leading to erosion of cartilage and bone, which is replaced by fibrous tissue (pannus). In pulmonary fibrosis, granulocytes initially appear in the alveolar spaces; however, the lung parenchyma, where fibrosis ultimately occurs, is infiltrated by macrophages and lymphocytes. Thus, there are parallels between atherosclerosis and these other inflammatory diseases.If the injurious agent or agents are not removed or nullified by the inflammatory response and the inflammation progresses, the response changes from a protective to an injurious response. Such constant or repetitive injury can stimulate each tissue to repair or wall off the damage by means of a fibroproliferative response, which, when excessive, diminishes the functional capacity of the tissue or organ and becomes part of the disease process.

INSTABILITY AND RUPTURE OF PLAQUE

Chronic inflammatory responses are often associated with specific types of injurious or granuloma-inducing agents. In most patients myocardial infarctions occur as a result of erosion or uneven thinning

and rupture of the fibrous cap, often at the shoulders of the lesion where macrophages enter, accumulate, and are activated and where apoptosis may occur.[36] Degradation of the fibrous cap may result from elaboration of metalloproteinases such as collagenases, elastases, and stromelysins.[37] Activated T cells may stimulate metalloproteinase production by macrophages in the lesions, which promotes plaque instability and further implicates an immune response. These changes may also be accompanied by the production of tissue-factor procoagulant and other hemostatic factors, further increasing the possibility of thrombosis. Stable advanced lesions usually have uniformly dense fibrous caps. The potentially dangerous lesions are often nonocclusive and thus difficult to diagnose by angiography, yet at autopsy active inflammation is evident in the accumulation of macrophages at sites of plaque rupture.[34] Macrophage accumulation may be associated with increased plasma concentrations of both fibrinogen and C-reactive protein, two markers ofinflammation thought to be early signs of atherosclerosis Plaque rupture and thrombosis may be responsible for as many as 50 percent of cases of acute coronary syndromes and myocardial infarction.

ROLE OF SMOOTH MUSCLE

Smooth-muscle cells have different embryonic origins, depending on the segment of the arterial system involved. In some vertebrates,

smooth-muscle cells in the upper portion of the thoracic aorta are derived from a neuroectodermal source, whereas those in the abdominal aortaare derived from a mesenchymal source. Although likely, this has not been confirmed in humans. The smooth-muscle cells of coronary arteries appear to originate from a third precursor population in the intracardiac mesenchyme. The existence of these different lineages suggests that smooth muscle in different parts of the arterial tree may respond differently to the stimuli that generate atherosclerotic lesions at each of these sites.

THE ROLE OF THE MATRIX

Smooth-muscle cells in the media of arteries, as well as in lesions, are surrounded by different types of connective tissue. In the media of arteries, the matrix consists largely of type I and III fibrillar collagen, whereas in the lesions of atherosclerosis it consists largely of proteoglycan, intermixed with loosely scattered collagen fibrils.

When cultured human arterial smooth-muscle cells are plated on collagen in fibrillar form, the collagen inhibits cell proliferation by up-regulating specific inhibitors of the cell cycle. In vivo degradation of the collagen by collagenase, or migration away from this inhibitory environment, may allow the smooth-muscle cells to respond to mitogenic stimuli and replicate, as they do when they are cultured on nonfibrillar, monomeric collagen. Other matrix molecules, such as fibronectin and

heparan sulfate, may be involved, because they can also inhibit the cell cycle, and cell–matrix interactions can lead to the expression of chemokines by macrophages. If these interactions were to occur in arteries, they could profoundly influence the inflammatory and fibroproliferative response. Thus, the matrix that surrounds the cells is not neutral and may determine whether they remain quiescent or multiply in response to growth factors.

C-REACTIVE PROTEIN AND ROLE IN ATHEROSCLEROSIS

C-reactive Protein (**CRP**) is an acute-phase protein produced by the liver in response to inflammation or infection. Because inflammation is considered an etiologic factor in cardiovascular events such as myocardial infarction (MI) and **stroke**, recent studies have looked at inflammation markers as potential predictors of risk for these events.

The inflammatory marker CRP is one of the most powerful independent predictors of myocardial infarction, stroke, and vascular death in a variety of settings, with prognostic value extending across various ethnic groups and in men and women in different age groups. More recently, elegant work by Ridker and colleagues[38] demonstrated that CRP may be a better predictor of future cardiovascular events than low-density lipoprotein (LDL) cholesterol and that baseline CRP evaluation adds prognostic value to the conventional Framingham risk assessment.

The link between CRP and atherosclerosis was initially suggested to be that of a "surrogate biomarker" vs. a mediator of atherosclerosis. This view has been recently revisited, with observations suggesting that CRP has a direct effect to promote atherosclerotic processes and endothelial cell inflammation. .

EFFECTS OF CRP ON MACROPHAGE LDL UPTAKE

. Uptake of LDL by macrophages is an important process contributing to plaque progression. Recent evidence suggests that CRP directly promotes native LDL uptake into macrophages, a process that is ET-1 dependent and inhibited during coincubation with the $ET_{A/B}$ receptor blocker bosentan

. EFFECTS OF CRP ON FIBRINOLYTIC PARAMETERS

. Endothelial cells are the major source of plasminogen activator inhibitor-1 (PAI-1), and PAI-1 serves to inhibit endogenous fibrinolysis, promoting atherothrombosis and progression of acute coronary syndromes. Recent evidence suggests that incubation of human coronary artery endothelial cells with CRP results in a time- and dose-dependent increase in secreted PAI-1 antigen, PAI-1 activity, intracellular PAI-1 protein, and PAI-1 mRNA.

EFFECTS OF CRP ON VASCULAR SMOOTH MUSCLE CELLS AND ANGIOTENSIN RECEPTOR REGULATION

Angiotensin II is one of the most important proinflammatory molecules, capable of promoting diverse proatherosclerotic processes at the level of the endothelium and VSM. The angiotensin type 1 receptor (AT_1-R) is a key atherosclerotic switch facilitating ANG II-induced reactive oxygen species (ROS) production, VSM cell migration, proliferation, and vascular remodeling. Given the central importance of AT_1-R in the development and clinical course of atherosclerosis, we recently evaluated the effects of CRP on AT_1-R and associated pathophysiological processes [40]. CRP potently upregulates AT_1-R mRNA and protein and increases the number of AT_1-R binding sites in VSM cells. This effect is not related to a change in AT_1-R mRNA stability, because the half-life of AT_1-R transcript was similar after incubation with actinomycin-D. Additionally, in VSM cells in vitro, CRP markedly stimulated cell migration and proliferation, with an effect approaching 75% of that noted with the pro-typical stimulant PDGF. The effects of CRP on VSM cells appear to be closely related to the expression of AT_1-R, because they were inhibited by losartan, an angiotensin receptor blocker. CRP also augmented ANG II-induced VSM cell migration and proliferation, further supporting a functional relationship between CRP and ANG II in mediating VSM cell pathology. In VSM cells, CRP increased basal ROS production and potentiated the effects of ANG II on ROS formation. These effects were

also inhibited by losartan, indicating that increased CRP-mediated ROS formation in VSM cells was related, in part, to increased AT_1-R expression. Last, in an in vivo model of carotid balloon angioplasty, CRP exposure facilitated AT_1-R expression, with resultant increases in neointimal formation, VSM migration, and proliferation and promoted collagen and elastin production, key matrix proteins in the vessel wall. These effects were attenuated by angiotensin receptor blockade with losartan. Therefore, CRP exerts direct proatherosclerotic effects at the level of the VSM (in addition to the endothelium), in part via increased AT_1-R expression and signaling. No effect of CRP was found on AT_2-R, which may be vasculoprotective in certain settings. Likewise, we did not observe an effect of CRP on ANG II release.

EFFECT OF CRP ON BONE MARROW DERIEVED ENDOTHELIAL PROGENITOR CELL

Postnatal neovascularization is a process that is vital to the compensatory physiological response in chronic ischemia. Myocardial ischemia provides a potent stimulus to angiogenesis and the subsequent development of collateral vasculature that maintains and/or revitalizes cardiac tissue. The mobilization and differentiation of bone-marrow derived endothelial progenitor cells (EPCs) has recently been shown to be important in this process of neovascularization [41]. Recently, the number and migratory activity of circulating EPCs has also been shown to

inversely correlate with risk factors for coronary artery disease. In this vein, recent work suggests that EPCs incubated with human recombinant CRP, at concentrations known to predict adverse vascular outcomes, exhibited decreased survival and increased apoptosis [42]. This reduction in EPC cell number was dose dependent, and at a CRP concentration of 20 μg/ml, there was an ~80% reduction in cell number at 7 days. Additionally, EPCs incubated with human recombinant CRP exhibited decreased expression of endothelial cell-specific markers Tie-2 and endothelial cell-specific lectin, indicating an effect of CRP to inhibit EPC differentiation. CRP also caused a significant decrease in EPC eNOS mRNA expression after 24 h of incubation. These observations extend the proatherogenic effects of CRP, beyond the endothelium and VSM to the bone marrow and the systemic response in chronic ischemia..

A growing body of evidence implicates CRP as a powerful risk marker for diverse cardiovascular and metabolic diseases. Initially, this association was suggested to be a surrogate one, wherein CRP functioned to highlight increased levels of vascular inflammation and, in this fashion, identify patients at heightened risk of atherothrombosis. Thus CRP may not just be a marker of atherosclerosis and coronary events, but also a mediator of this disease because it contributes to the substrate underlying lesion formation, plaque rupture, and coronary thrombosis.

TREATMENT OF RISK FACTORS:

It is useful to group the cardiovascular risk factors that have emerged into two categories: (1) those modifiable by lifestyle and/or pharmacotherapy, and (2) those that are essentially unmodifiable . The weight of evidence supporting various risk factor differs. For example, hypercholesterolemia and hypertension indubitably predict coronary risk, but other so-called nontraditional risk factors, such as levels of homocysteine, lipoprotein (a) [Lp(a)], or infection, remain controversial. It is worth distinguishing further between factors that actually participate in the pathogenesis of atherosclerosis and those that may merely serve as markers of risk without themselves playing a primary role in pathogenesis..

LIPID DISORDERS

Abnormalities in plasma lipoproteins and derangements in lipid metabolism rank as the most firmly established and best understood risk factors for atherosclerosis.Current national guidelines recommend cholesterol screening in all adults. The screen should include a fasting lipid profile [total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol]. Dietary measures, including specific consultation by practitioners with training in nutrition, should be offered to all patients with hyperlipidemia .Additional risk factors for coronary heart disease or when the HDL level

is below 40 mg/dL. Many patients with established atherosclerosis fall into this category. Such individuals should receive particular encouragement to adopt life-style measures such as diet and exercise aimed at increasing their HDL levels.The addition of drug therapy to dietary and other nonpharmacologic measures to reduce the risk of atherosclerotic events in asymptomatic patients without manifest vascular disease remains unsettled. In asymptomatic patients with heterozygous familial hypercholesterolemia, LDLlowering by pharmacologic measures reduces atherosclerosis in both men and women. The West of Scotland Study established that lipid lowering with the HMG-CoA inhibitor pravastatin can effectively reduce cardiac events and total mortality in a cohort of patients with hypercholesterolemia but without prior myocardial infarction . The recent AFCAPS/TexCAPS Study showed that treatment with lovastatin similarly reduced coronary events in patients without previous myocardial infarction but with "average" total and LDL cholesterol levels and somewhat decreased HDL levels.Although the role of drug therapy in primary prevention of the manifestations of atherosclerosis remains incompletely defined, abundant evidence establishes the benefit of drug therapy in patients with hypercholesterolemia and established coronary artery disease . A number of well-designed and -executed large-scale clinical trials have now shown that treatment with statins reduces recurrent myocardial infarction, reduces strokes, and lessens the need for revascularization

or hospitalization for unstable angina pectoris. These studies have enrolled patients in numerous countries on at least three continents and encompass individuals with clearly elevated levels of cholesterol and those with "average" total and LDL cholesterol levels. Lipid-lowering therapies do not appear to exert their beneficial effect on cardiovascular events by causing a marked "regression" of obstructive coronary lesions. Angiographically monitored studies of lipid lowering have shown at best a modest reduction in coronary artery stenoses over the duration of study. Yet these same studies consistently show substantial decreases in coronary events. These results suggest that the mechanism of benefit of lipid lowering does not require a substantial reduction in the fixed stenoses. Rather, the benefit may derive from "stabilization" of atherosclerotic lesions without decreased stenosis. Such stabilization of atherosclerotic lesions and the attendant decrease in coronary events may result from the egress of lipids or by favorably influencing aspects of the biology of atherogenesis discussed in . In addition, as sizeable lesions may protrude abluminally rather than into the lumen, shrinkage of such plaques might not be apparent on angiograms.The benefit of LDL lowering by HMG-CoA reductase inhibitor (statin) therapy on cardiovascular events seems to require 6 to 24 months of treatment. Improvement of vasomotor responses to endothelial-dependent vasodilators occurs much more rapidly, requiring 6 months or less. Thus, HMG-CoA reductase inhibitors may act by two or more

mechanisms on the arteries of hypercholesterolemic individuals. The relatively rapid improvement in endothelial-dependent vasomotion may reflect enhanced production or reduced destruction of the endogenous vasodilator nitric oxide at the level of the arterial endothelium. Reduction in the thrombotic complications of atherosclerosis, such as myocardial infarction or unstable angina, probably requires more prolonged treatment to effect removal of lipid from deeper within the atheroma,yielding improvements in the biology underlying plaque destabilization.Our current understanding of the mechanism by which elevated LDL levels promote atherogenesis relates to oxidative modification of these particles within the artery wall, promoting formation of macrophage-derived foam cells and providing a stimulus for inflammation . These concepts have given rise to considerable interest in the possibility that antioxidants, either dietary or pharmacologic, might reduce atherogenesis. Considerable experimental evidence supports this notion. In addition, many observational studies show a correlation of antioxidant consumption and reduced cardiovascular risk. Rigorous, controlled clinical trial evidence, however, has not yet proven the effectiveness of antioxidant therapy, whether dietary or with supplements of vitamins or drugs, for prevention or treatment of atherosclerosis. Indeed, controlled trials with □-carotene have demonstrated no reduction in cardiovascular events. For these reasons, as its efficacy remains speculative, it is premature to consider

antioxidant administration as a replacement for established therapies. Furthermore, general use of such treatments, particularly in lower risk individuals, should await the results of rigorous prospective studies designed to define the doses, appropriate patient groups, and evaluate the possibility of adverse or unwanted effects of antioxidants.

HYPERTENSION

The preponderance of epidemiologic data supports a relationship between hypertension and atherosclerotic risk. Clinical trial evidence available since the 1970s established that pharmacologic treatment of hypertension can reduce the risk of stroke and heart failure. However, clinical trial evidence demonstrating reduced risk of coronary events due to antihypertensive therapy has lagged. At present, the combined weight of the evidence supports a reduction in coronary risk by antihypertensive therapy. Some of the difficulty in demonstrating this benefit may derive from the potentially adverse effects of certain classes of antihypertensive drugs on the lipid profile, notably, thiazide diuretics and beta-blocking agents. Indeed, studies of patients with previous myocardial infarction or reduced left ventricular function have shown that treatment with angiotensin-converting enzyme (ACE) inhibitors can reduce the risk of coronary events, an unanticipated outcome. Therefore "lipid-neutral" antihypertensive agents such as ACE inhibitors or β_1-adrenergic blocking agents merit consideration in patients with other risk factors for coronary artery disease or with established atherosclerosis.

DIABETES MELLITUS AND INSULIN RESISTANCE

Most patients with diabetes mellitus die of atherosclerosis and its complications. Secular trends towards aging of the population and increased girth will make type 2 (noninsulin-dependent) diabetes mellitus an increasing public health problem in the coming years. The criteria for diagnosis of diabetes have recently undergone revision. Currently, a fasting plasma glucose level of (125 mg/dL) establishes the diagnosis of diabetes. In the intermediate range, plasma glucose levels between (110 and 125 mg/dL) indicate impaired fasting glucose. Thus, fasting glucose> (110 mg/dL) indicates abnormal glucose tolerance. These definitions based on fasting plasma glucose alone obviate the need for performing glucose tolerance tests. A major feature of elevated cardiovascular risk in patients with type 2 diabetes probably relates To the abnormal lipoprotein profile associated with insulin resistance known as *diabetic dyslipidemia*. While diabetic patients may often have LDL cholesterol levels near average, the LDL particles tend to be smaller and denser and thus more atherogenic . Other features of diabetic dyslipidemia include low HDL and elevated triglycerides. Establishing that strict glycemic control reduces the risk of macrovascular complications of diabetes has proven much more elusive than the established beneficial effects on microvascular complications such as retinopathy or renal disease. In the absence of clear-cut evidence that tight glycemic control reduces coronary risk in diabetic patients,

attention to other aspects of risk in this patient population assumes even greater importance. In this regard, recent clinical trials have demonstrated unequivocal benefit of HMG-CoA reductase inhibitor therapy in diabetic patients, including those with "average" LDL cholesterol levels. Having diabetes places patients in the same risk category as those with established atherosclerotic disease. These guidelines establish a target LDL cholesterol level of (100 mg/dL) for the patient with diabetes.

MALE GENDER/POSTMENOPAUSAL STATE

Observational studies have verified excess coronary risk in males compared with premenopausal females. After menopause, however, coronary risk accelerates in women. At least part of the apparent protection against coronary heart disease in premenopausal women derives from their relatively higher HDL levels compared with those of men. After menopause, HDL values fall in concert with increased coronary risk. Estrogen therapy lowers LDL cholesterol and raises HDL cholesterol, changes that should decrease coronary risk. A multitude of observational studies has suggested that estrogen-replacement therapy (ERT) reduces coronary risk. Substantial experimental data support the biologic plausibility of a beneficial effect of estrogen in reducing atherosclerotic events, but a number of potential confounding factors render clinical trials necessary to establish the cardiovascular benefits of

ERT. In men, high-dose estrogen treatment caused excess mortality, probably due to increased thromboembolic complications.

The recently reported Heart and Estrogen/Progestin Replacement Study (HERS) has highlighted the need for clinical trial evidence to substantiate the observational and experimental data regarding estrogen's beneficial effects on the vasculature and lipid profile. In this trial, postmenopausal female survivors of acute myocardial infarction were randomized to an estrogen/progestin combination or to placebo. This study showed no overall reduction in recurrent coronary events in the active treatment arm. Indeed, early in the 5-year course of this trial, there was a trend toward an actual increase in vascular events in the treated women. As in the previous Coronary Drug Project trial, the excess events may have resulted from an increase in thromboembolism. HERS does not definitively exclude a potential benefit of other combinations of estrogens with progestins or a benefit of estrogens alone in patients lacking a uterus. A more prolonged follow-up might have disclosed an accrual of benefit in the treatment group, as the excess events appeared in the first years of the trial in the treated group. Moreover, drugs of the selective estrogen receptor modulator class might dissociate the increased risk of breast and/or uterine cancer from cardiovascular benefit. This possibility will likewise require randomized clinical trial evidence evaluating coronary events to validate widespread application. In the recent clinical trials with HMG-CoA reductase

inhibitors, women, when included, have derived benefits at least commensurate with those seen in men. Data from HERS itself showed that application of lipid- lowering therapy to female survivors of myocardial infarction lagged far behind guidelines. Choices regarding ERT in postmenopausal women remain complex. Physicians should work together with women to provide information and help weigh the risks and benefits of ERT, taking personal preferences into account.

DYSREGULATED COAGULATION OR FIBRINOLYSIS

Thrombosis ultimately causes the gravest complications of atherosclerosis. The propensity to form thrombi and/or to lyse clots once they form could clearly influence the manifestations of atherosclerosis. Thrombosis provoked by atheroma rupture and subsequent healing maypromote plaque growth,. Certain individual characteristics can influence thrombosis or fibrinolysis and have received attention as potential coronary risk factors. For example, fibrinogen levels correlate with coronary risk and provide information regarding coronary risk independent of the lipoprotein profile. Elevated fibrinogen levels might promote a thrombotic diathesis. Alternatively, fibrinogen, an acute-phase reactant, may serve as a marker of inflammation rather than directly participating in the pathogenesis of coronary events.The stability of an arterial thrombus depends on the balance between fibrinolytic factors, such as plasmin, and inhibitors of the fibrinolytic system, such as

plasminogen activator inhibitor (PAI) 1. Certain genotypes of the PAI-1 gene appear to correlate with increased coronary risk. Yet,

overall, the levels of tissue plasminogen activator and PAI-1 in plasma have not proven to add information beyond the lipid profile to assessment of cardiovascular risk. Likewise, the role of Lp(a) as a modulator of fibrinolysis remains controversial. Apo Lp(a) has high homology to plasminogen but lacks the enzymatic activity of this fibrinolytic molecule. Thus, Lp(a) might antagonize fibrinolysis, serving as a type of "dominant negative" competitor of plasminogen. However, in vivo evidence for this mechanism, and, indeed, the independent contribution of Lp(a), is clouded by difficulties in standardizing the assays and the highlypolymorphic nature of this protein in humans.

HOMOCYSTEINE

A large body of literature suggests a relationship between hyperhomocysteinemia and coronary events. Several mutations in the enzymes involved in homocysteine accumulation correlate with thrombosis and, in some studies, coronary risk. Although thrombosis and atherosclerosis seem intimately linked, direct evidence of an atherogenic effect of hyperhomocysteinemia in humans remains weak. The role of hyperhomocysteinemia in atherosclerotic complications, however, has important practical implications. The plasma level of homocysteine can vary with diet. Nutritional supplementation with folic

acid can lower homocysteine levels in many individuals. A substantial portion of the elderly population has only a marginal sufficiency of folate intake. Recommending a diet rich in folate or consumption of multivitamin supplements containing folic acid should be considered in individuals with atherosclerosis out of proportion to traditional or established risk factors and with elevated levels of homocysteine. The possibility that folate treatment might mask pernicious anemia should be considered when advising such supplementation. No clinical trial evidence currently establishes a reduction in coronary events in patients with hyperhomocysteinemia treated with folate.

INFECTION/INFLAMMATION

Recent years have witnessed a resurgence of interest in the possibility that infections may cause or contribute to atherosclerosis. A spate of recent publications has furnished evidence in support for a role of *Chlamydia pneumoniae,* cytomegalovirus, or other infectious agents in atherosclerosis and restenosis following coronary intervention. Some microorganisms exist in human atherosclerotic plaques. However, seroepidemiologic evidence for an association between infection with various agents and atherosclerosis remains inconclusive. Several ongoing large trials of antibiotic treatment in survivors of myocardial infarction may provide support for an etiologic or contributory role of microbial infection in recurrent coronary events.

LIFE-STYLE MODIFICATION

It is important to counsel patients regarding the health risks of tobacco use and provide guidance regarding smoking cessation. Likewise, physicians should advise all patients about prudent dietary and exercise habits for maintaining ideal body weight. . Obesity, particularly the male pattern of centripetal or visceral fat accumulation, can promote an atherogenic dyslipidemia characterized by elevated triglycerides, a low HDL level, and glucose intolerance. Physicians should encourage their patients to take responsibility for behavior related to modifiable risk factors for development of premature atherosclerotic disease. Conscientious counseling and patient education may forestall the need for pharmacologic measures intended to reduce coronary risk.Adoption of hygienic life-style changes to ameliorate coronary risk entails little expense or possibility of adverse effects. In contrast, pharmacotherapy can prove costly. Although lipid-lowering drugs such as the HMG-CoA reductase inhibitors have proven exceedingly well tolerated in clinical trials, the use of these or other lipid-lowering agents could produce adverse reactions in some individuals. The decision to initiate drug treatment for reduction of risk of atherosclerotic events requires careful consideration, particularly in the setting of "primaryprevention" or in patients without known atherosclerotic disease. In this regard, it is prudent to consider not only the LDL cholesterol but also the individual patient's global cardiovascular risk.

For example, an individual with an average LDL but a low HDL, hypertension, and a family history of premature coronary artery disease might warrant initiation of drug therapy more than an individual with the same LDL level in the absence of the other risk factors. The calculation of coronary risk includes taking gender, smoking history, and systolic blood pressure into account, in addition to plasma cholesterol levels. This policy illustrates how estimations of global risk may be applied to optimize decisions regarding initiation of drug therapy to prevent atherosclerotic events

CAROTID DOPPLER:

Carotid atherosclerotic plaque usually involves the internal carotid artery within 2 cm of the carotid bifurcation. This location is readily amenable to exploration by ultrasound.Sonography can assess plaque morphology such as hemorrhagic plaque which is a source of increased thromboembolic events. The diagnostic work up of carotid disease has changed dramatically over the past two decades.Carotid sonography has largely replaced angoiography as the most noninvasive and costeffective screening method to assess suspected extracranial carotid atherosclerotic disease.Angiography is now reserved for those patients in whom the ultrasound or MRA is inadequate. Other carotid ultrasound applications are evaluation of carotid bruitsmonitoring progress of known atherosclerotic disease assessment during or after endarterectomypreoperative

screening prior to major vascular surgeryNon atherosclerotic diseases can be evaluated including follow up of carotid dissection evaluation of Takayasu's arteritis assessment of malignant carotid artery invasion.

PLAQUE CHARECTERIZATION :

Atheromatous carotid plaques should be carefully evaluated to determine plaque extent, location, surface contour and texture as well as assessment of luminal stenosis.

Plaque texture is generally classified as being homogenous or heterogenous. Homogenous plaques has a uniform echo pattern and a smooth surface.The uniform echotexture corresponds pathologically to dense fibrous connective tissue.Calcified plaque produces posterior acoustic shadowing and is common in asymptomatic individuals. Heterogenous plaque has a more complex echo pattern and has one or more focal sonolucent areas. Hetrogenous plaque is characterized pathologically by intraplaque hemorrhage.Sonography accurately determines the prescence of intraplaque hemorrhage. A "Swiss Cheese" pattern with multiple sonolucent areas is charecterestic of intraplaque hemorrhage. Sonographic changes that suggest plaque ulceration include a focal depression or break in the plaque surface or an anechoic area within the plaque which extends to the plaque surface without an

intervening echo between the vessel lumen and the anechoic plaque region

PLAQUE MORPHOLOGY ON CAROTID DOPPLER .

Type 1- predominantly echolucent plaque, with a thin echogenic cap

Type-2- substantially echolucent with small areas of echogenicity

Type 3- predominantly echogenic with small areas of echolucency

Type 4- uniformly echogenic

MATERIALS AND METHODS

This study was conducted in forty dyslipidemic patients who attended the Medicine OPD at PSG Hospitals.

AIM OF THE STUDY

The aim of the study is to determine wether CRP concentrations were correlating with the prescence of atherosclerotic plaques in a dyslipidemic population.

INCLUSION CRITERIA

The inclusion criteria were as follows.

Fasting serum lipid values;

Total cholesterol > 200mg/dl

Triglycerides > 150mg/dl

EXCLUSION CRITERIA

Age < 18 and >70 years

CRP >10mg/l[represents clinically relevant inflammation]

HDL > 70mg/dl

DETERMINATION OF C-REACTIVE PROTEIN

- Specimen Collection

Only disposable glass tubes were used for sample collection

Blood samples were collected with aseptic precautions into a plain glass tube

- Method- Latex agglutination
- Carotid Doppler

In the supine position, with the head turned away from the sonographer and the neck extended with mild rotation, each patient systematically underwent ultrasonography of the extracranial carotid arteries by use of a duplex system.The protocol consisted of study of the right and left common and internal carotid arteries [including bifurcations] with use of 8-11 mega hertz scanning frequency in B - mode . Plaque was defined as an echogenic structure encroaching the vessel lumen with a distinct area 50% greater than the intimal plus medial thickness of neighbouring sites.

PROFORMA OF THE STUDY

NAME AGE ADDRESS

IP NO-

OP NO GENDER

DATE

EXAMINATION

BP PULSE AUSCULTATION

INVESTIGATIONS

CHOLESTEROL C-REACTIVE PROTEIN

LEVELS

BLOOD SUGAR

BLOOD UREA

SERUM CREATININE CAROTID DOPPLER

FINDINGS

TRIGLYCERIDES

RESULTS AND ANALYSIS

TABLE SHOWING CRP LEVELS AND CAROTID DOPPLER FINDINGS

SERIAL NO	AGE [YEARS]	SEX	CRP LEVELS(mg/dl)	CAROTID DOPPLER
1	45	F	0.6	NO PLAQUE
2	55	M	0.6	NO PLAQUE
3	48	F	0.6	NO PLAQUE
4	50	F	0.7	NO PLAQUE
5	55	F	0.6	NO PLAQUE
6	60	M	0.8	NO PLAQUE
7	58	M	0.7	NO PLAQUE
8	51	M	0.6	NO PLAQUE
9	60	F	0.7	NO PLAQUE
10	62	M	0.8	NO PLAQUE
11	41	F	0.6	NO PLAQUE
12	54	M	0.6	NO PLAQUE
13	49	F	0.7	NO PLAQUE
14	43	F	0.6	NO PLAQUE
15	54	F	0.6	NO PLAQUE
16	43	M	0.7	NO PLAQUE
17	45	M	0.6	NO PLAQUE
18	55	M	0.6	NO PLAQUE

19	65	F	0.7	NO PLAQUE
20	56	F	0.6	NO PLAQUE
21	54	M	0.6	NO PLAQUE
22	55	M	0.7	NO PLAQUE
23	56	F	0.6	NO PLAQUE
24	65	F	0.6	NO PLAQUE
25	58	M	0.7	1CM x 2.1MM-POSTERIOR WALL 0F LEFT ICA
26	65	M	0.6	3CM x 2 MM-POSTERIOR WALL OF LEFT ICA
27	68	M	1.2	2.5MM x 1.3CM-POSTERIOR WALL OF RIGHT CCA
28	54	F	0.6	2MM x 3MM -POSTERIOR WALL OF LEFT CCA
29	67	M	1.1	1MM x 2MM-POSTERIOR WALL LEFT ICA-ORIGIN
30	58	M	1.2	1.6CM x 3 CM-POSTERIOR WALL-LEFT ICA ORIGIN
31	60	M	0.6	1.5CM x 3MM-ORIGIN OF LEFT ICA

32	62	M	0.8	1CM x 3CM-POSTERIOR WALLOF RIGHT ICA
33	67	F	1.2	1CM x 4CM-ANTERIOR WALL OF RIGHT CCA
34	69	M	1.2	2CM x 3CM-POSTERIOR WALL OF LEFT ICA ORIGIN AND 1CM x 3CMM POSTERIOR WALL OF RIGHT ICA
35	65	F	0.6.	2MM x 3CM ORIGIN OF CCA RIGHT SIDE
36	66	M	0.5	1CM x 1CM POSTERIOR WALL OF RIGHT CCA ORIGIN
37	58	F	1.2	3CM x 1CMORIGIN OF RIGHT ICA
38	65	M	0.6	3MM x 2MM-ANTERIOR WALL OF RIGHT CCA
39	65	M	0.6	1CM x 1CM DISTAL RIGHT CCA
40	63	F	0.8	2CM X 1CM DISTAL LEFT CCA

MEAN CRP LEVELS IN DYSLIPIDEMIC PATIENTS WITHOUT PLAQUE AND WITH PLAQUE

CASE[DYSLIPIDEMIC PATIENTS]	NO OF CASES	MEAN CRP LEVELS(MG/DL)
WITHOUT PLAQUE	24	0.617
WITH PLAQUE	16	0.869

STATISTICS

The results of forty patients were analysed.Twenty four of the patients did not have plaques .Sixteen of them had plaques.The mean CRP of both the set of patients were calculated.The standard deviation w as calculated. The results were analysed by subjecting it to the null hypothesis. The null hypothesis was rejected and the p value was found to be significant.[p value - <0.001 / t value-3.9].So CRP was found to correlate with prescence of atherosclerosis in dyslipedemic patients.

DISCUSSION

CORRELATION OF CRP WITH ATHEROSCLEROSIS IN DYSLIPEDEMIC PATIENTS

In this study the relationship between CRP and carotid atherosclerosis was evaluated and was found to correlate.

The Bruneck study[4] was a study done to study the etiology and epidemiology of carotid atherosclerosis. In this study 125 men and 125 women were selected who were between the ages 40-79 years.Their risk factor profile were evaluated. The risk factors which were evaluated included diabetes,hypertension and smoking.A biochemical evaluation of other risk factors was also performed.It included lipid levels,acute phase reactants such as CRP, D-Dimer.lipoprotein-a.Every patient underwent a carotid doppler study of the common carotid arteries, origins of the internal and external carotid arteries.

The conclusion drawn from the study was that atherosclerosis was of two types.One type was a chronic progressive lesion .This was a marker for early atherosclerosis.The risk factors which correlated positively for these type of lesions included diabetes,hypertension,dyslipidemia .The

levels of CRP was also found to correlate with carotid atherosclerosis in this study.

Otherwise there are very few studies comparing CRP with carotid atherosclerosis. There have been other studies comparing CRP with atherosclerosis in other vascular territories such as the coronaries and peripheral limb vessels.A few of these studies are being quoted here.

Studies have revealed that CRP has been associated with cardiac conditions such as chronic stable angina as well as acute events associated with atherosclerosis such as the spectrum of acute coronary syndromes compromising of conditions such as unstable angina,acute myocardial infarction and non ST elevation myocardial infarction.

In one study by Nader Rifas,[45] Rana Joubran 100 patients were selected who had angiographically proven coronary artery disease.Each patient had a minimum of one vessel involvement with at least a 50% block.These patients were evaluated for risk factors for coronary atherosclerosis and were subjected to other biochemical investigations which included C-Reactive Protein.The results of the study showed that C-Reactive proteins levels were increased in the patients who had angiographically proven coronary artery disease compared to the controls.But in this study C –Reactive protein levels did not correlate with the severity of the atherosclerosis that is C-Reactive protein levels were not any higher in patients with a more severe block compared with

patients with a lesser degree of block.This study supports the fact that C-Reactive protein is a marker of diffuse atherosclerosis.

In a study by Heinrich T,Schulte H,[5] 929 patients were selected from patients who were admitted into a coronary rehabilitation unit.The extent of their coronary atherosclerosis was evaluated by means of a coronary angiogram, the extent of extracranial cerebrovascular disease by means of B-mode ultrasound and the extent of peripheral vascular disease by means of baseline and stress oscillography.The results of this study showed that C-Reactive Protein levels correlated with the prescence of cerebrovascular and peripheral vascular disease.

In another study by Thompson SG,Kienast SG[1] about 3500 patients who had chronic stable angina were selected.All these patients underwent a angiographic procedure. They were also subjected a series of biochemical analysis which included CRP and other tests such as fibrinogen , tissue plasminogen activator inhibitor, protein c and protein s .The patients were then prospectively followed up for a period of time and the end point was the occurrence of acute events such as myocardial infarction and sudden cardiac deaths. The results of the studies showed that CRP correlated with the occurrence of acute coronary events in patients with chronic stable angina .

In a study by Paul.M.Ridker [2] the association between C-Reactive Protein and Peripheral Vascular Disease was studied in which 144 apparently healthy men who underwent baseline CRP measurements and were subsequently followed .up.The results of the studies showed that CRP levels were higher at baseline in those patients who went on to develop peripheral vascular disease.

CONCLUSION

This study was conducted on fourty dyslipidemic patients at PSG Hospitals, Coimbatore.

All patients were subjected to a biochemical test in the form of C-Reactive Protein and simultaneously subjected to a carotid Doppler study by means of ultrasound.

The C-Reactive Protein levels among patients with atherosclerotic plaques was found to be higher than in patients without plaques.[p value< 0.001].The mean value of the CRP in patients without carotid plaques was found to be 0.61 and the mean values in the patients with carotid plaques was found to be0.86.

Literature review showed few studies which showed an association between CRP levels and carotid atherosclerosis . There were other studies which showed association between CRP levels and atherosclerosis in other vascular beds such as the coronary circulation and the peripheral circulation.

The present study showed the correlation of C-Reactive Protein levels with the prescence of carotid atherosclerosis.

Whether C-Reactive Protein can be used routinely in patients as a risk factor for., atherosclerosis is still a matter of debate although many trials have proved the association of C-Reactive Protein

with atherosclerosis in various vascular beds such as coronary,cerebral and peripheral vascular beds.Most of the studies in relation to C-Reactive Protein has been done in patients with coronary atherosclerosis , more studies are required to prove it's association in other vascular beds.

It can thus be concluded that C-Reactive Protein is a marker of carotid atherosclerosis in patients with dyslipidemia which is an important risk factor for atherosclerosis.

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