

A New Insight into Pathogenesis of Cardiovascular Diseases: Stress Induced Lipid Mediated, Vascular Diseases

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Abstract

Based on my clinical experience and knowledge gained through extensive research in this area, I have come up with a hypothesis which sheds more light in the pathogenesis of cardiovascular diseases. Atherosclerosis is implicated as playing the key role in the pathogenesis of cardiovascular diseases which involves large and medium sized arteries. There is now evidence that atherosclerosis is an immuno-inflammatory process.

My hypothesis is that chronic psychosocial stress is the main trigger for the systemic inflammation which results by activation of Hypothalamus-Pituitary-Adrenal (HPA) axis and Sympathetic-Adrenal-Medulla (SAM) axis. This stress response sets into motion innate immune response, initiating a cascade of events which include: Release of neuro-endocrine transmitters, endothelial dysfunction, and increased permeability of micro vascular circulation and increased delivery of free fatty acids in circulation among others. Liver responds by increased Low Density Lipoproteins (LDL) production which continuously enters the arteries, excess LDL is transformed into oxidized low density lipoproteins (ox LDL). ox LDL goes through pattern recognition and is recognized as antigen. Adaptive immunity is activated. ox LDL is pro oxidant, results in inflammation, reactive oxygen species are released causing oxidative stress. This causes atherosclerosis in large and medium sized arteries and tissue damage in organs sub served by micro vasculature. Hence the process being systemic inflammation is not limited to large and medium sized arteries but is global in reach involving the entire vasculature. The pathogenesis of these disorders may be classified as "stress induced, lipid mediated vascular inflammation".

This article will review stress and pathophysiology of stress, pathophysiology of cardiovascular diseases which includes endothelial dysfunction, pathogenesis of atherosclerosis, inflammation in atherosclerosis, and current concepts of diseases comprising cardiovascular diseases, including the risk factors for CVDs. It enters the stage of hypothesis based on the knowledge gained. It discusses microcirculation, and goes over disorders involving microcirculation. Oxidative Stress is reviewed followed by a brief summary. It winds up with discussion, management and conclusion.

Abbreviations

HPA: Hypothalamic Pituitary Adrenal; SAM: Sympathetic Adrenal Medulla; CNS: Central Nervous System; BDNF: Brain Neurotropic Factor; PSA-NCAM: Polysciated Neural cell Adhesion Molecule; tpa: Tissue Plasminogen Activator; NFkB: Nuclear Factor kB; CRF: Cortico Trophin Releasing Factor; ACTH: Adrenocorticotrophin Hormone; IL₆: Interleukin -6; APR: Acute Phase Response; NO: Nitric Oxide; ROS: Reactive Oxygen Species; eNOS: e Nitrogen Oxide Synthase; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; CVD: Cardiovascular Disease; CHD: Coronary Heart Disease; ABI: Ankle Brachial Index; PAD: Peripheral Arterial Disease; RAS: Renal Artery Stenosis; ASCVD: Atherosclerotic Cardiovascular Disease; BP: Blood Pressure; DM: Diabetes Mellitus; CV: Cardiovascular; CRP: C Reactive Protein; ECS: Endothelial cells; Met S: Metabolic Syndrome; CKD: Chronic kidney disease; COPD: Chronic Obstructive Pulmonary Disease; NAFLD: Non Alcoholic Fatty Liver Disease; RNS: Reactive Nitrogen Species; AF: Atrial Fibrillation; oxLDL: Oxidized Low Density Lipoprotein; CAC: Coronary Artery Calcium; CIMT: Carotid Intima Media Thickness; MSNA: Muscle Sympathetic Nerve Activity

Review

Stress

The term stress has changed its meaning from that of a non-specific body response to a 'monitoring system of internal and external cues' that is a modality of reaction of the mammalian Central Nervous System (CNS) which is critical to the adaptation of the organism to its environment [1]. Other working definition of stress is a physiological response that serves as a mechanism of mediation on linking any given stressor to its target organ effect. Stress begins in the brain and affects the brain as well as rest of the body [2].

Stress response

Most stressors are psychosocial and they set the stage for stress response. Cognitive appraisal mechanism determines affect (felt emotion). Once appraisal is made efferent impulses project to highly sensitive emotional anatomy in the limbic system especially in hippocampus to trigger visceral effector mechanism, Impulses also project to areas of neocortex concerned with neuromuscular behavior. Stress hormones and other mediators such as neuro transmitters, cytokines and other hormones are essential for adaptation to

challenges of daily life as well as to major life stresses. This process has been called “allostasis”, that is maintaining stability or homeostasis through change. When mediators of allostasis like cortisol and adrenaline are released in response to stressor or lifestyle factors such as diet, sleep and exercise they promote adaptation and survival and are generally beneficial.

Chronic stress can promote and exacerbate pathophysiology through the same systems that are dysregulated. The burden of chronic stress and accompanying changes in personal behaviors (smoking, eating too much, drinking, poor quality sleep otherwise referred to as “lifestyle”) is called allostatic load.

Brain region such as hippocampus, prefrontal cortex and amygdala respond to acute and chronic stress. The adaptive plasticity of chronic stress involves many mediators including glucocorticoids, excitatory amino acids, endogenous factors such as Brain Neurotrophic Factor (BDNF), Polysciated Neural Cell Adhesion Molecules (PSA-NCAM) and Tissue Plasminogen Activator (tPA) [3].

In response to a stressor physiological changes are set into motion to help the individual cope with the stressor. However chronic activation of the stress response which includes the Hypothalamus – Pituitary-Adrenal (HPA) axis and the Sympathetic-Adrenal Medullary (SAM) axis results in chronic production of glucocorticoids hormones and catecholamine’s.

Glucocorticoid receptors exposed on a variety of immune cells bind cortisol and interfere with the function of NF kB which regulates the activity of cytokine producing immune cells.

Adrenergic receptors bind epinephrine and nor-epinephrine and activate the cAMP response element binding protein, inducing the transcription of genes encoding for a variety of cytokines.

The changes in gene expression mediated by glucocorticoids and catecholamines can dysregulate immune function. The magnitude of stress associated immune dysregulation is large enough to have health implications [4].

Stress response is initiated and comprises of (neuro endocrine effector system) Sympathetic-Adrenal-Medullary System (SAM), which is under the control of central neural pathways. Another component of stress response i.e. physiological system that regulates the biologic reactions elicited in response to challenging stimulus or stimuli is the Hypothalamus-Pituitary-Adrenal (HPA) axis. Both the HPA axis and SAM work in concert to coordinate adaptive response. Regulation of HPA axis occurs through negative feedback mechanism in which high levels of glucocorticoids suppress the release of corticotrophin releasing factor.

Hypothalamus –Pituitary Adrenal (HPA) axis

CNS is the highest point of origin of this stress response. Most chronic and prolonged somatic responses to stress are the result of the endocrine axes. Neural impulses from septal hippocampal complex descend to median eminence of hypothalamus which releases Corticotrophin Releasing Factor (CRF) into hypothalamus – hypophysial portal system which descends to anterior pituitary, which responds by releasing ACTH in the systemic circulation to its primary target organ, adrenal gland, which releases glucocorticoids into systemic circulation.

The effects of this result in increased glucose production-lipidogenesis, exacerbation of gastric irritation, increase urea

production, increased release of fatty acids into systemic circulation, increased susceptibility to atherosclerotic processes, increased susceptibility to non-thrombotic myocardial necrosis, exacerbation of herpes simplex, increased ketone body production, appetite suppression and depression.

There is also increased mineralo-corticoids, thyroid hormones, vasopressin and oxytocin production.

Neuro endocrine mechanism by Sympathetic -Adrenal – Medullary (SAM) axis activation

This response can be activated by psychosocial stimuli. Highest point of origin is dorso medial amygdallar complex, downward flow of neural impulses which pass to lateral and posterior hypothalamus. From here neural impulses descend through thoracic spinal cord, converging at celiac ganglion, then to adrenal medulla. Catecholamines are released. Nor epinephrine and epinephrine release, results in increase in generalized adrenergic somatic activity functionally identical to direct sympathetic innervation, except this takes 20-30 seconds delay in onset for measurable effect. This prolongs sympathetic response.

Effects on the body are, increased blood pressure, increased blood supply to brain, increased heart rate, increased cardiac output and stimulation of skeletal muscles, increased fatty acids, triglycerides, cholesterol, increased release of endogenous opioids, decreased blood flow to kidneys, gastro- intestinal system and skin, increased risk of hypertension, thrombus formation, angina, arrhythmias and death. If excessive, activation may lead to neuromuscular dysfunction, increased limbic excitation and heightened emotional arousal [2].

There are several articles which demonstrate the role of stress in various disease processes.

The article published in *Annals of The New York Academy of Sciences* describes that stress promotes adaptation but prolonged stress leads over time to wear and tear on the body (allostatic load), short term adaptation but long term damage. Allostatic load leads to impaired immunity, atherosclerosis, obesity, bone demineralization and atrophy of nerve cells in the brain. Many of these processes are seen in major depressive illnesses, and may be expressed in other chronic anxiety disorders [5].

The article published in *Post graduate medical Journal* describes strong association between depression and cardiovascular diseases. Different degree of association between depression and IHD have been shown in many epidemiological and observational studies which have shown raised cardiovascular mortality and morbidity rates in patients with diagnosis of depression. In longitudinal studies of initially healthy community residents without a history of IHD, depression has been associated with a relative risk between 1.5 and 2 for the subsequent development of IHD, myocardial infarction and cardiac death over moderate to longer periods and is largely independent of traditional risk factors. Clinically significant depressive symptoms are found in 40-65% of patients after myocardial infarction. The prevalence of depression is also increased in patients with stable IHD and in patients who undergo coronary artery bypass surgery. Acute and chronic mental stress is shown to increase the risk of IHD. Psychosocial stress and conditions such as depression, anxiety and a specific personality type may cause direct pathophysiological changes. There is evidence linking new psychiatric condition with hormonal and hematopoietic abnormalities. These include hypothalamus-pituitary axis activation,

adrenergic hyper activity, platelet abnormalities leading to increased adhesiveness, raised fibrinogen levels, endothelial dysfunction and raised left ventricular mass and the progression of carotid atherosclerosis [6].

A small study published in *Circulation* describes that mental stress has been linked to increased morbidity and mortality in coronary artery disease due to atherosclerosis progression. They demonstrated that brief episodes of mental stress similar to those encountered in everyday life may cause transient endothelial dysfunction in healthy young individuals. This may represent a mechanistic link between mental stress and atherogenesis [7].

The study published in *American Journal of Psychiatry* describes that significant life stress including early life stress a major risk factor for development of major depression, once manifested major depression has been associated with enhanced tonic activation of the innate immunity system including increased plasma pro inflammatory cytokines such as interleukin (IL) -6. In non-depressed individuals exposure to psychosocial stress has been associated with increased plasma IL -6 response as well as activation of nuclear factor (NF) - κ B, a transcription factor that serves as lynchpin in the inflammatory signal cascade.

The study findings suggested that male major depression patients with early life stress may clinically exhibit stress induced increases in inflammatory markers that are further exacerbated by exposure to acute stress. These findings indicate that depressed patients with increased early life stress exhibit both a baseline hyper inflammatory state coupled with a hyper responsive inflammatory response to stress which together may contribute to medical co morbidities associated with major depression and inflammation, such as cardiovascular diseases.

Previous stress exposure has been shown to sensitize subsequent immune responses to immune challenge and therefore the findings may result from an interaction between major depression and early life stress.

Sympathetic nervous system activation has been shown to enhance inflammatory responses and major depression patients with early life stress have been shown to exhibit enhanced sympathetic nervous system response to stress challenge [8].

The article published in *Brain, Behavior and Immunity* describes the relationship of stress and the inflammatory response. The author reviews the subject of neuro inflammation. In response to psychological stress or certain physical stressors an inflammatory process may occur by release of neuropeptides especially Substance P (SP) or other inflammatory mediators from sensory nerves and the activation of mast cells or other inflammatory cells. Central neuropeptides particularly Corticosteroids Releasing Factor (CRF) and perhaps SP as well, initiate a systemic response by activation of neuro endocrinological pathways such as the sympathetic nervous system, hypothalamus pituitary axis and the renin angiotensin system with the release of stress hormones (i.e. catecholamine's, corticosteroids, growth hormones, glucagon and renin). These together with cytokines induced by stress initiate Acute Phase Response (APR) and the induction of acute phase proteins, essential mediators of inflammation. Neither central nervous system nor epinephrine may also induce the APR perhaps by macrophage activation as may lipopolysaccharide which the author postulates induces cytokines from hepatic Kupffer cells subsequent to an enhanced absorption from the gastrointestinal tract during psychological stress. The brain may initiate

or inhibit the inflammatory process. The inflammatory response is contained within the psychosocial stress response which evolved later. Moreover the same neuropeptides (CRF and possibly SP as well) mediate both Stress and inflammation. Cytokines evoked by either Stress or inflammation response may utilize similar somatosensory pathways to signal the brain, other instances whereby stress may induce inflammatory changes are reviewed in the article. The author postulates that repeated episodes of acute or chronic psychogenic stress may result in atherosclerosis in the arteries or chronic inflammatory changes in other organs as well [9].

Stress recently has shown to play an important role in onset of cardiovascular diseases, immunological disorders and pathophysiological consequences of normal ageing. The stress is involved in the onset, development, course and progress of many diseases [10].

There is increased association of cancer and decreased immune response to pathogens in chronic stress [11].

Endothelial Activation/Dysfunction

Endothelium in Normal Vascular Homeostasis

Endothelium is a simple monolayer. The healthy endothelium is optimally placed and is able to respond to physical and chemical signals by production of a wide range of factors that regulate vascular tone, cellular adhesion, thrombo resistance, smooth muscle cell proliferation and vessel wall inflammation. The importance of the endothelium was first recognized by its effects on vascular tone. This is achieved by production and release of several vasoactive molecules that relax or constrict the vessel as well as by response to and modification of circulating vasoactive mediators such as bradykinin and thrombin.

This vaso motion plays a direct role in the balance of tissue oxygen supply and metabolic demand by regulation of vessel tone and diameter and is also involved in the remodeling of vascular structure and long term organ perfusion.

The endothelium modulates vaso motion by release of vasodilator substances. Nitric Oxide (NO) is an endothelium derived relaxing factor. NO is generated from L-arginine by the action of endothelial NO Synthase (eNOS) in the presence of cofactors. This gas diffuses to the vascular smooth muscle cells and activates guanylate cyclase which leads to cGMP-mediated vasodilatation. The endothelium also mediates hyperpolarization of vascular smooth muscle cells via NO – independent pathway, which increases potassium conductance and subsequent propagation of depolarization of vascular smooth muscle cells to maintain vascular tone. Prostacyclin, derived by the action of cyclooxygenase system is another endothelium derived vasodilator that acts independent of NO.

The endothelium modulates vasomotion not only by release of vasodilator substances but also by an increase in constrictor tone via generation of endothelin and vasoconstrictor prostanoids as well as conversion of angiotensin 1 to angiotensin 11 at the endothelial surface.

In normal vascular physiology NO plays a key role to maintain the vascular wall in a quiescent state by inhibition of inflammation, cellular proliferation and thrombosis. This is in part achieved by s-nitrosylation of cysteine residue in a wide range of proteins which reduce their biologic activity. The target proteins include the

transcription factor NF κ B, cell cycle – controlling proteins and proteins involved in generation of tissue factor. Furthermore NO limits oxidative phosphorylation in mitochondria.

Endothelial Activation and atherosclerosis

What is generally referred to as endothelial dysfunction should more appropriately be considered as endothelial activation, which may eventually contribute to arterial disease when certain conditions are fulfilled. Endothelial activation represents a switch from a quiescent phenotype towards one that involves the host defense response. Indeed most cardiovascular risk factors activate molecular machinery in the endothelium that results in expression of chemokines, cytokines and adhesion molecules designed to interact with leukocytes and platelets and target inflammation to specific tissues to clear microorganisms.

The fundamental change involved in the process is a switch in signaling from an NO – mediated silencing of cellular processes toward activation by redox signaling. Reactive Oxygen Species (ROS) in the presence of superoxide dismutase, lead to generation of hydrogen peroxide which like NO can diffuse rapidly through the cell and react with cysteine groups in proteins to alter their function. However because of the different chemistry involved, this results in very different consequences such as phosphorylation of transcription factors, induction of nuclear chromatin remodeling and transcription genes and protease activation. There is eNOS uncoupling which results in superoxide formation, if the key co- factor is not present or generation of hydrogen peroxide if the substrate L-arginine is deficient.

Chronic production of ROS may exceed the capacity of cellular enzymatic and non-enzymatic anti-oxidants and thus contribute to vascular disease by induction of sustained endothelial activation.

An important source of ROS is probably the mitochondria, in which production of ROS and diminishing capacity of mitochondrial superoxide dismutase are typically carefully balanced during oxidative phosphorylation. This may be disturbed during hypoxia or conditions of increased substrate delivery such as occurs in obesity- related metabolic disorders or type 2 diabetes which are characterized by hyperglycemia and increased circulating fatty acids.

Endothelial activation and redox signaling may contribute to atherogenesis

Endothelial injury and repair

Prolonged and/ or repeated exposure to cardiovascular risk factors can ultimately exhaust the protective effects of endogenous anti-inflammatory systems within endothelial cells. As a consequence endothelium not only becomes dysfunctional but endothelial cells can lose integrity, progress to senescence and detach into the circulation.

Circulating markers of such endothelial cell damage include endothelial micro particles derived from activated or apoptotic cells and whole endothelial cells. The markers have been found to be increased in both peripheral and coronary atherosclerosis as well as other inflammatory conditions associated with increased vascular risk such as rheumatoid arthritis and systemic lupus erythematosus. Circulating endothelial micro particles and endothelial cells can be quantified.

Clinical correlation

Most if not all risk factors that are related to atherosclerosis and cardio vascular morbidity and mortality including traditional and non-traditional risk factors were also found to be associated with endothelial dysfunction. Many of the risk factors including hyperlipidemia, hypertension, diabetes and smoking are associated with over production of reactive oxygen species or increased oxidative stress. By reacting with NO, reactive oxygen species may reduce vascular NO bioavailability and promote cellular damage. Increased oxidative stress is considered a major mechanism involved in the pathogenesis of endothelial dysfunction and may serve as common mechanism of the effect of risk factors on the endothelium [12].

Both physical exercise and mental stress, 2 of the main triggers of an increase in myocardial demand are associated with epicardial coronary endothelial dysfunction. On the other hand diverse studies indicated an association between the presence of coronary micro vascular endothelial dysfunction and angina pectoris in patients with angiographically normal coronary arteries. Endothelial Dysfunction is a reversible disorder. Observation that several pharmacological interventions that improve endothelial function are associated with decrease in cardiovascular events independent of risk factors share a concept that cardiovascular risk factors share a common pathway that leads to endothelial dysfunction such as oxidative stress [13].

Pathogenesis of atherosclerosis

Atherosclerosis is a multifocal, smoldering immuno-inflammatory disease of medium-sized and large arteries fuelled by lipids.

Endothelial cells, leukocytes and intimal smooth muscle cells are the major players in the development of disease.

Atherogenic stimuli

Among many cardiovascular risk factors, elevated plasma cholesterol is unique in being sufficient to drive development of atherosclerosis. Other risk factors such as hypertension, diabetes, smoking, male gender and possibly inflammatory markers e.g. C-reactive protein, cytokines and so on appear to accelerate a disease driven by atherogenic lipoproteins, the first of which being LDL. The importance of risk factors beyond cholesterol is documented by great disparity in the expression of clinical disease.

Protective factors

Alcohol, exercise and High Density Lipoprotein (HDL) and its major apo A-1 confer protection against disease caused by atherogenic modification of LDL and promote “reverse cholesterol transport” which slows plaque progression.

Susceptibility

The susceptibility to atherosclerosis differs not only in individuals with similar risk factor scores but also among different arterial segments from same individual (Arterial susceptibility).

Cellular component of Atherosclerosis

Endothelial cells

Atherosclerotic lesion begins to develop under an intact but leaky, activated and dysfunctional epithelium. Later endothelial cells may

vanish and de-endothelialized (denuded) areas appear with or without platelets adhering to the exposed sub-endothelial tissue.

Depending on size and concentration plasma molecules and lipoprotein particles extravasate through the leaky and defective endothelium into the sub-endothelial space, where potentially atherogenic lipoproteins are retained and modified (oxidized) and become cytotoxic, pro-inflammatory, chemotactic and pro-atherogenic. The mechanism for this modification is unknown but could be oxidation mediated by myeloperoxidases, lipooxygenase, and/or Nitric Oxide Synthase (NOS).

Nitric oxide is a potent oxidant produced by both endothelial cells and macrophages that appear to exert both protective and atherogenic effect. NO produced by NOS in macrophages is pro-atherogenic.

The endothelium becomes activated by atherogenic and pro-inflammatory stimuli and the expression of adhesion molecules, primarily vascular cell adhesion molecule-1 (VCAM-1), are up-regulated and monocytes and T cells are recruited. Other adhesion molecules intracellular adhesion molecule-1, E Selectin and P Selectin probably contribute to recruitment of blood-borne cells to the atherosclerotic lesions.

Endothelial dysfunction as assessed clinically (impaired nitric oxide mediated vasodilatation) predicts clinical events caused by atherosclerosis. It is indeed thought provoking that mere presence of risk factors is associated with endothelial dysfunction not only in atherosclerosis susceptible arteries but also in arteries that are relatively resistant to atherosclerosis e.g. (the brachial artery).

Leukocytes

One of the earlier responses in atherogenesis is focal recruitment of circulating monocytes and to a lesser extent T lymphocytes. The persistence of this cellular response seems to underlie disease progression. B lymphocytes and plasma cells are rare in intimal plaque but may be abundantly present in adventitia next to advanced intimal disease. Activated mast cells may be found both in plaque and adventitia, particularly in culprit lesions causing acute ischemic events. Neutrophils are rare in the complicated atherosclerosis.

Mere adhesion to the endothelium of blood-borne cells is not enough to arrive in the lesions, trans-endothelial migration is required. One or more chemokines are necessary. Endothelial cells, smooth muscle cells and macrophages all contribute to over-expression of MCP-1 (Monocyte Chemoattractant Protein).

Within the intima monocytes differentiate into macrophages and internalize atherogenic lipoproteins via so-called scavenger receptors. The development of lipid-loaded macrophages containing massive amounts of cholesterol esters (foam cells) is a hallmark of both early and late atherosclerotic lesions. With continuing supply of lipoproteins, the macrophages eat until they die, in contrast to native LDL receptor, scavenger receptors are not down-regulated by cellular cholesterol accumulation.

The death of macrophages by apoptosis and necrosis contributes to soft and destabilizing lipid-rich core within the plaque. On the other hand macrophages may under appropriate conditions (low LDL and high HDL) shrink by effluxing cellular cholesterol to extra-cellular HDL via membrane transporter, the initial step in "reverse cholesterol transport". Aside from scavenger function macrophages also possess destabilizing and thrombotic properties by expressing matrix metalloproteinases and tissue factor [14].

Immune activity is ongoing in atherosclerotic lesions

Innate immunity in atherosclerosis

Early involvement of monocytes / macrophages is the most prominent cellular component of the innate immunity response during atherogenesis.

The recruitment of mononuclear phagocytes involves attachment to activated endothelial cells by the leukocyte adhesion molecules, several protein mediators, specialized cytokines known as chemokines, direct cell migration of monocytes into the intima. Maturation of monocytes into macrophages their multiplication and production of many mediators ensues.

Monocytes entry occurs not just during the initial stages but continues even in established lesions.

Hyperlipidemia elicits a profound enrichment of pro-inflammatory subset of monocytes in the mouse. These pro-inflammatory monocytes home to atherosclerotic lesions, where they propagate the innate immune response by expressing high levels of pro-inflammatory cytokines and other macrophage mediators including matrix metalloproteinases.

Recent evidence has also highlighted the potential participation of mast cells in atherosclerosis.

Many links exist between lipoproteins and innate immunity. Modified lipoproteins interact with scavenger's receptors and may thus send pro-inflammatory signals and oxidized phospholipids derived from modified lipoproteins may also drive inflammation.

There is also link between thrombosis and inflammation. A major protein mediator of coagulation, thrombosis can elicit the expression of pro-inflammatory cytokines from vascular endothelium and smooth muscle cells. Platelets when activated can secrete preformed pro-inflammatory cytokines and exteriorize and shed multi-potent pro-inflammatory stimulus CD 40- ligand. Platelets can also release a pro-inflammatory mediator known as (MRP-8/14). MRP-8/14 can bind TLR4 activating innate immunity through this pattern recognition receptor. This ligand can also promote endothelial cell apoptosis a process implicated in plaque thrombosis. These observations tighten the link between inflammation and thrombosis suggesting an intimate interlacing of these 2 convergent pathways in atherosclerosis [15].

Adaptive immunity

Accumulating evidence suggests a key regulating role of adaptive immunity in atherosclerosis and its complications. Interacting with a special subset of mononuclear phagocytes specialized in antigen presentation known as dendritic cells.

T lymphocytes encounter antigens and mount a cellular immune response. The dendritic cells populate atherosclerotic plaques and regional draining lymph nodes, where they can present antigens to T cells with co-stimulating molecules that incite these key afferent nodes for adaptive immunity. Putative antigens that stimulate T cells in the context of atherosclerosis include certain heat shock proteins, components of plasma lipoproteins and potentially microbial structures as well. The clone of T cells that recognizes T cells in this context will proliferate to amplify the immune response. Upon renewed exposure to the specific antigen these T cells produce cytokines and trigger inflammation and some T cells have mechanisms specialized for killing cells. This amplification accounts for the delay in

the typical adaptive immune response that is slower and much more structurally specific than “fast and blunt” innate immune response [15].

Cardiovascular Diseases

Cardiovascular Disease generally refers to atherosclerosis involving a group of arterial territories which belong to large and medium sized vessels such as diseases of coronary arteries, diseases of aorta, diseases of carotid arteries and peripheral arteries which includes visceral arteries, renal arteries, upper and lower extremity arteries.

A host of risk factors are associated with these conditions such as hypertension, dyslipidemias, diabetes- mellitus, ageing, cigarette smoking, obesity, metabolic syndrome and newly emerging risk factors i.e. hs CRP, Carotid Intima Media Thickness (CIMT), Coronary Artery Calcium Score (CAC) and Ankle Brachial Index (ABI).

Other risk factors are atherogenic diet, physical inactivity, positive family history of premature coronary artery disease, and male gender.

Cardiovascular disease is single largest cause of death over last decade worldwide. An estimated 80 million Americans (nearly one in three) have CVD. Coronary heart disease and stroke are currently the number one and number four (later recently quoted number five) causes of mortality respectively.

Cardiovascular diseases can be categorized as macro vascular diseases

Coronary artery disease

The main focus is on disease involving epicardial arteries key role being played by atherosclerosis. This presents clinically as Acute Coronary Syndrome (ACS), Non ST Segment Myocardial Infarction (NSTEMI), and ST Segment Elevation Myocardial Infarction (STEMI). The vast majority of ACS should now largely be thought of as expression of a common pathophysiology along a continuum of severity.

This may also present as stable ischemic heart disease. Studies have demonstrated that stable coronary heart disease presents more indolently due to gradual occlusion of a coronary vessel from a largely stable lipid poor plaque but ACS are most often due to acute disruption (or” rupture “) of a form of plaque that is biologically quite distinct from the more benign stable plaque.

Risk factors for coronary heart disease are age, sex, diabetes, hypertension, Left ventricular hypertrophy, dyslipidemia low HDL, high LDL, and cigarette smoking, CHD risk equivalents, emerging risk factors C-Reactive protein, ABI, CAC and CIMT [16].

Diseases of the aorta

Diseases of the aorta in majority of the patients are caused by atherosclerosis and may lead to development of aneurysm, which may involve abdominal aorta, thoracic aorta or both.

There is a prevalence of 5-7% among men and 1% among women older > than 65 years on population screening. The major risk associated with AAAs is that of rupture. Among participants in the United Kingdom Small Aneurysm Trial who suffered ruptured AAA 25% died before reaching the hospital, another 50% died at the hospital prior to aortic repair and overall 30 day survival was just 11%.

Risk factors for abdominal aortic aneurysm are smoking, male gender, age, family history of abdominal aortic aneurysm, hypertension, hyperlipidemia and atherosclerosis [16].

Carotid artery disease

The vast majority of carotid artery disease is atherosclerotic in origin. Population surveys utilizing carotid artery Doppler ultrasonography have found significant carotid stenosis in 5-7% of female adults and 7-9% of male adults > 65 years of age.

The proportion of stroke events attributable to carotid disease is difficult to depict but estimates are in the range of 10-20%.

Nearly one half of stroke events in patients with high grade asymptomatic carotid artery stenosis are attributable to non-carotid etiologies such as lacunes or carotid embolism.

Symptomatic ICA stenosis presents a high risk of stroke. A TIA predicts a 10-20% stroke risk in the first 90 days after the event, a risk that is highest in the first week. Among patients with TIA the presence of ipsilateral > 50% stenosis predicts a higher risk of stroke within seven days of symptom onset. A reflection of the high early risk is that the benefit of CEA in patients with symptomatic ICA Stenosis falls sharply after the first two weeks.

Cerebral small vessel disease accounts for approximately 25% of acute ischemic strokes. The term “small vessel disease” encompasses all the pathological processes that affect small vessels of the brain including small arteries and arterioles but also capillaries and small veins. The two most common types are arteriosclerosis (e.g. hypertensive disease) and amyloid angiopathy. Amyloid angiopathy is characterized by amyloid protein in the walls of small to medium sized arteries and arterioles predominantly located in lepto meningeal space and cortex. New imaging of small vessel disease includes multiple micro hemorrhages, large hematomas, white matter lesions (leukoaraiosis) and lacunar infarcts [16].

Peripheral arterial disease

Lower extremity peripheral arterial disease

Peripheral arterial disease (PAD) is primarily the result of atherosclerosis in the arteries of the lower extremities and is frequently associated with atherosclerosis in all vascular distributions. Presence of PAD confers significant risk of cardiovascular morbidity and mortality primarily due to stroke (from cerebrovascular atherosclerosis) and myocardial infarction (Myocardial infarction from coronary atherosclerosis).

3% of individuals in the United States 40-59 years old have abnormal ABI indicative of PAD, 8% of those 60-69 and 19% of those > 70 years old also are afflicted with total of 8.4 million individuals in the country with PAD.

In addition to age risk factors for PAD are similar to those of coronary artery disease: diabetes, tobacco use, hypertension, and dyslipidemia. Diabetes and tobacco each confer a three to four fold increase in the risk of developing PAD [16].

Visceral artery disease

Among patients with atherosclerotic disease the presence of stenosis of at least one of the visceral vessels is common. A duplex ultrasound study found that 17.5% of patients over 65 years of age had more than

70% stenosis of at least one mesenteric artery. An angiographic study of patients with peripheral arterial disease demonstrated that 27% of the subjects had 50% stenosis of the celiac trunk or Superior mesenteric artery. More than 3% had significant stenosis of both vessels.

In addition among patients with severe renal artery stenosis, one half have concomitant significant mesenteric artery stenosis.

Risk factors for visceral arterial disease include tobacco, hyperlipidemia hypertension and diabetes mellitus [16].

Renal Artery Disease

Renal Artery Stenosis (RAS) is common among patients with atherosclerotic disease. Several studies have confirmed that the prevalence of renal artery disease is 25-34% among patients referred for cardiac catheterization who undergo renal angiography. The prevalence of one artery at least in 50% stenosis range from 11-23% of patients referred for cardiac catheterization.

Atherosclerosis is the most common cause of renal artery stenosis and is responsible for approximately 90% of cases. RAS is a progressive disease.

There are several pathways by which Reno vascular disease may result in renal parenchymal damage. Decreased nitric oxide availability, increased endothelin production and activation of the RAS contribute to ischemic nephropathy. Ischemia also results in tubular injury and eventually interstitial fibrosis. Risk factors for renal artery stenosis include hyperlipidemia, diabetes and smoking [16].

Risk factors for cardiovascular disease

Hypercholesterolemia / Dyslipidemia

An estimated 16.2% of adults residing in the United States have total cholesterol levels of 240 mg /dl or greater, placing them at increased risk of cardiovascular disease (CVD). Until recently the risk was assessed and recommendations were outlined based on guidelines set by Adult Treatment Program 111 published in 2001 and updated in 2004. The guidelines were based on a large body of evidence which demonstrated that lowering LDL-C results in statistically significant reductions in cardiovascular events.

In late 2013 ACC /AHA provided revised guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. The goals were to prevent cardiovascular diseases and improve the management of people who have the disease through professional education and research. The clinical practice recommendation was updated for the treatment of blood cholesterol levels to reduce Atherosclerotic Cardiovascular Disease (ASCVD) risk using data from Randomized Controlled Trials (RCTs), and systematic reviews and meta-analysis of RCTs. For the guidelines, ASCVD includes coronary heart disease, stroke and peripheral arterial disease, all of presumed atherosclerotic origin.

These studies provided the rationale for RCTs which in turn demonstrated that lowering cholesterol levels reduced ASCVD events and there by establishes a central causal role of atherogenic cholesterol containing lipoprotein particles particularly LDL in the genesis of CHD and ASCVD. The RCTs identified in the systematic evidence review indicated a consistent reduction in ASCVD events from 3-hydroxy 3 methylglutaryl co- enzyme A reductase inhibitors (Statins)

therapy in secondary and primary prevention populations with the exception of ASCVD event reduction in those with New York Heart Association (NYHA) class II-IV heart failure or receiving hemodialysis [16, 17].

Hypertension

CVD including stroke is the most common cause of death and disability in developed countries. Hypertension is one of the most important modifiable risk factors for CVD. Hypertension affects 25% of the adult population of the world. Primary hypertension (Essential or idiopathic hypertension) accounts for about 90% of all causes of hypertension.

Approximately 76 million Americans have hypertension about one in 3 of the adult population. In a study conducted in 1999-2000, 40% of persons were normotensive, 30% pre hypertensive and 30% were hypertensive. There has been an increase in the prevalence of hypertension in the United States, from 1988-1994 (25%) to 2005-2008 (33%) with a consequent increase in the hypertension related mortality. The prevalence of hypertension increases with age, so that over 50% of the population above the age of 55 years has hypertension and in the 75+ age group the prevalence is 70-80%.

Etiology

Increased sympathetic nervous system activity, over production of sodium -retaining hormones and vasoconstriction (endothelin and thromboxane), deficiencies of vasodilators such as prostaglandins and nitric oxide, increase or inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) may contribute in pathogenesis of hypertension. The concept that structural and functional abnormalities in the vasculature - including endothelial dysfunction, increased oxidative stress, vascular remodeling and decreased compliance may antedate hypertension and contribute to the pathogenesis.

Sympathetic nervous system

Increased sympathetic nervous system activity increase blood pressure and contributes to the development and maintenance of hypertension through stimulation of the heart, peripheral vasculature and kidneys causing increased cardiac output, increased vascular resistance and fluid retention.

Autonomic imbalance (increased sympathetic tone accompanied by reduced parasympathetic tone) has also been associated with many metabolic, hemodynamic, trophic and rheologic abnormalities that result in increased CV morbidity and mortality.

Increased sympathetic activity and / or reduced parasympathetic activity increases heart rate, stroke volume, cardiac output, peripheral resistance, nor epinephrine and epinephrine secretion by adrenal medulla and renin secretion by activation of the B₂-adrenergic receptors on the juxtaglomerular apparatus of the kidney. All of these effects raise BP.

Renal sympathetic nerve stimulation is increased in hypertension patients, including renal tubular Na⁺ and water reabsorption resulting in intravascular volume expansion and increased BP. Chronic sympathetic stimulation induces vascular remodeling and left ventricular hypertrophy by actions of nor- epinephrine on its receptors.

Vascular reactivity

Hypertensive patients manifest greater vasoconstrictor response to infused nor-epinephrine than normotensive controls. The expected down regulation of nor-adrenergic receptors in response to increased circulating nor-epinephrine levels does not occur in hypertensive patients, resulting in enhanced sensitivity to nor-epinephrine, increased peripheral resistance and BP elevation. Centrally acting sympatholytic agents and alpha and beta adrenergic antagonists are effective in reducing BP in patients with essential hypertension, thus providing indirect clinical evidence for the importance of sympathetic mechanisms in the maintenance of hypertension.

Exposure to stress increases sympathetic outflow and repeated stress induced vasoconstriction may result in vascular hypertrophy leading to increased peripheral resistance and BP [16].

Diabetes mellitus

Diabetes is the seventh leading cause of death in the United States and associated with an increased hazard for cardiovascular, non-cardiovascular cancer death. The overall risk of death in patients with diabetes is twice that of patients without diabetes.

Epidemiology

Diabetes Mellitus (DM) affects 28.5 million people (8.3%) of the population in the United States. The frequency of diabetes increases with age. More than 25% of patients > 65 years have diabetes. Each year in the United States two million new cases develop in individuals > 20 years of age. Diabetes is the leading cause of kidney failure, non-traumatic lower limb amputation and new cases of blindness. It is a major determinant of heart disease and stroke. DM is a metabolic disorder characterized by insufficient insulin secretion necessary to maintain normal plasma glucose values.

Type 2 DM is increasing in prevalence, particularly young people in the United States. According to search for diabetes in youth, a multi registry tracking all new cases of DM in adolescence and children 0-19 years old 15,600 patients were diagnosed with Type 1 DM and 3,600 with Type 2 DM from 2002-2005. During each year 18.6 per 100,000 new cases of Type 1 DM were diagnosed in adolescents ages 10-19. In the same age group 85 per 100,000 new cases of Type 2 DM were diagnosed [16].

Smoking

Tobacco use is associated with significant morbidity and mortality. Cigarette smoking is a major modifiable risk factor in the development of atherosclerosis, myocardial infarction and mortality after revascularization.

Pathophysiology

There are several mechanistic pathways, whereby cigarette smoking leads to the development of atherosclerosis and Cardiovascular Disease (CVD). These include vasomotor and endothelial dysfunction, inflammatory response, adverse effects on lipids and changes in coagulation.

Endothelial dysfunction is a precursor to atherosclerosis and exposure to tobacco impairs nitric oxide availability and endothelial function. Smoking cessation leads to improved endothelial function as well as reduced arterial stiffness. Acute exposure to cigarette smoking

can cause acute vasospasm and increased total coronary vascular resistance and increased myocardial oxygen demand.

Inflammation plays a role in the activation of leukocytes and development of atherosclerosis. Circulating leukocytes, and multiple inflammatory markers including C-Reactive Protein (CRP), interleukin -6 and tumor necrosis factor are elevated in smokers. Exposure to tobacco smoke also increases the Vascular Cell Adhesion Molecule (VCAM) -1, Intercellular Adhesion Molecule (ICAM) -1 and E-selectin, thus increasing cell to cell interaction, recruitment of leukocytes and development of atherosclerosis. The fibrinolytic / thrombogenic balance is impaired in smokers. Platelets become activated, and fibrinogen levels are increased. Endothelium produces less tissue plasminogen activator and plasminogen activator inhibitor-1. There is reduced thrombolytic capacity during acute coronary event in smokers.

Cigarette smoking is associated with a less favorable lipid profile with smokers having high total cholesterol, triglycerides, Low Density Lipoprotein Cholesterol (LDL-C) Levels and low High Density Lipoprotein Cholesterol (HDL-C).

There are increased levels of oxidized LDL-C particles and antibodies against LDL-C in smokers. Smoking cessation improves levels of HDL-C but not the LDL-C number or particle size [16].

Metabolic Syndrome (Met S)

The Met S comprises a constellation of inter-related risk factors of metabolic origin that promotes the development of diabetes mellitus and atherosclerotic CVD.

The most widely recognized are atherogenic dyslipidemia, elevated blood pressure and elevated plasma glucose.

The 2005 American Heart Association (AHA) /National Heart and Lung, and Blood Institute update of the NCEP definition defines the presence of Met S on the basis of demonstrating three or more of the following abnormalities:

Abdominal obesity as determined by a waist circumference > 88 cm in women and > 102 cm in men.

Elevated blood pressure based on a systolic blood pressure of 130 mmHg or greater and a diastolic blood pressure of 85 mmHg or greater or being on the anti-hypertensive treatment.

Low HDL cholesterol (HDL_C) defined as < 40 mg /dl in men or < 50 mg /dl in women or taking medications to raise HDL -C.

Elevated fasting triglycerides defined as 150 mg /dl or greater or taking medications to lower levels of elevated triglycerides or non-fasting triglycerides of 400 mg /dl or greater and

Impaired fasting glucose of 100 mg /dl or greater or taking medication to lower glucose levels. Alternatively a non-fasting glucose of 140 mg /dl or greater could be considered equivalent to this level for being defined as a criterion of Met S with 200 mg /dl or greater defining Diabetes.

Prevalence and Epidemiology

Data from US adults in 1999-2000 show a prevalence of Met S of 33.7% among men and 35.4% among women according to NCEP definition with higher estimates of 39.9% and 38.1% respectively using IDF definition.

Among US adults a twofold greater risk of mortality from CHD and CVD in persons with Met S was observed in the study. Even those with Met S but without diabetes and those with only one or two Met S risk factors are at increased risk of death from CHD and CVD. Moreover those with diabetes in the absence of CVD had a similar risk of total mortality as those with preexisting CVD hence supporting the concept of diabetes as CVD risk equivalent.

Nurses' Health Study has shown that among those with Met S age adjusted incidence rates of future CVD events were 3.4 and 5.9 per 1,000 per year for those with CRP levels of < 3 and > 3 mg /L

Increased levels of fibrinogen, plasminogen activator inhibitor-1 and other coagulation factors are seen in persons with Met S. A pro-inflammatory state exhibited by elevated cytokines (e.g. Tumor necrosis factor-alpha and interleukin-6) and acute phase reactants (e.g CRP, fibrinogen) is frequently seen in persons with Met S [16].

Obesity

Prevalence of obesity in US is 33.9 % of population. Importantly overweight and obese comprise over 68% of the population. Several CV risk factors track with obesity and contribute to increased risk of CVD events. Obese individuals are approximately three times more likely to have hypertension and Type 2 diabetes than normal weight individuals and they more often have dyslipidemias, metabolic syndrome and obstructive sleep apnea. Independent of the risk factors obesity conveys an increased risk of all-cause mortality, CV death, stroke and CHD. These associations are manifest even with obesity measured in adolescence.

Obese individuals are more prone to left ventricular hypertrophy, diastolic filling abnormalities atrial fibrillation and cardiomyopathy [16].

Ageing

Ageing an independent risk factor for CVD is associated with chronic inflammation. There is decreased availability of Nitric oxide (NO) mediator that inhibits vascular tone, thrombus and vascular inflammation. Decreased NO availability results in blunted endothelial dependent vasodilatation which leads to sequential oxidative and pro-inflammatory events that facilitate atherosclerosis. Increased intracellular oxidative stress is due to augmented expression of oxidant generating enzymes such as NADPH oxidase, xanthine oxidase and uncoupled NO Synthase, also to the down regulation of endothelial and oxidative enzymes. Oxidative stress causes modification of key proteins, facilitation of the production of endothelium dependent vasoconstrictor prostanoids and activation of stress response mechanisms. These events initiate a pro-inflammatory response, a key initial event in the genesis of the atherosclerotic plaque [18].

Diet

Despite major advances in medical therapies for reducing CV events diet and lifestyle changes remain the most effective ways to reduce the burden of CVD in the general public. Current dietary patterns along with decreasing physical activity have led to epidemics in obesity and diabetes. Obesity and diabetes are both major risk factors for CVD.

LDL-C levels are linearly related to an increasing CVD risk and LDL-C remains the primary lipoprotein target for CV risk reduction. The strongest dietary determinants of LDL-C levels are dietary

saturated fatty acids and trans fatty acids intake. HDL-C and triglycerides are also affected by dietary pattern and body weight [16].

Physical Activity

Regular exercise participation can decrease the risk of initial and recurrent cardiovascular events, presumably from multiple mechanisms, including anti-atherosclerotic, anti-ischemic, anti-arrhythmic, anti-thrombotic and psychological effects. Chronic aerobic exercise can result in moderate loss in body weight and moderate to large losses in body fat. Endurance exercise can promote decrease in blood pressure (particularly in hypertensives), total blood cholesterol serum triglycerides, and low density lipoprotein cholesterol and increase in the aerobic capacity and "anti atherogenic" "high density lipoprotein cholesterol sub fraction". Exercise also has favorable effects on glucose and insulin homeostasis, inflammatory markers (e.g C-reactive protein), coagulability, fibrinolysis and coronary endothelial function.

Because > 40% of the Cardiovascular risk reduction associated with exercise cannot be explained by changes in conventional risk factors, a cardio protective "vascular conditioning" effect has been proposed, including enhanced nitric oxide vasodilator function, improved vascular reactivity, altered vascular structure or combinations thereof. Decreased vulnerability to threatening ventricular arrhythmias and increased resistance to ventricular fibrillation have also been postulated to reflect exercise-related adaptations in autonomic control including reduced sympathetic drive and increased vagal tone [16].

Emerging risk factors

C - reactive protein

C - reactive protein (CRP) is a 110 kDa protein predominantly synthesized by hepatocytes in response to the inflammatory cytokines, interleukin (IL)-6 and IL -1.

CRP was the first acute phase protein to be described and is an exquisitely sensitive marker of inflammation and tissue damage. The acute phase response comprises the non-specific physiological and biochemical responses of endothermic animals to most forms of tissue damage, infection, inflammation and malignant neoplasia. In particular, the synthesis of a number of proteins is rapidly up regulated, principally in hepatocytes under the control of cytokines originally at site of pathology.

Circulating CRP concentration levels: In healthy young adults volunteer blood donors median concentration of CRP is 0.8 mg/l, the 90th centile is 3.0 mg/ l and 99 th centile is 10 mg/ l. Following an acute phase stimulus values may increase from less than 50 mcg/l to more than 500 mg/l that is 10,000 fold.

Plasma CRP is produced only by hepatocytes, predominantly under transcriptional control by the cytokine IL-6. De novo hepatic synthesis starts very rapidly after a single stimulus. Serum concentration rising above 5 mg/l by about 6 hours and peaking around 48 hours. The plasma half-life of CRP is 19 hours and is constant under all conditions of health and disease, so that sole determinant of circulating CRP is the synthesis rate, which thus directly reflects intensity of the pathological process (es) stimulating CRP production. When the stimulus for increased production completely ceases, the circulating CRP concentration falls rapidly at almost the rate of plasma CRP clearance. There is no seasonal variation in baseline CRP

concentration and remarkably the self-correlation coefficient of measurements repeated years apart is 0.5 mg/l which is comparable to that of cholesterol.

In selected general population of ostensibly healthy subjects, the median CRP value is slightly higher than among blood donors and tends to increase with age. In most though not all diseases, circulating value of CRP reflects ongoing inflammation and / or tissue damage much more accurately than do other laboratory parameters of the acute phase response, such as plasma viscosity and the erythrocyte sedimentation rate.

Importantly acute-phase CRP values show no diurnal variation and are unaffected by eating.

Liver failure impairs CRP production but no other inters current pathologies and very few drugs reduce CRP values unless they also affect the underlying pathology providing acute phase stimulus.

The CRP concentration is thus a very useful nonspecific biochemical marker of inflammation, measurement of which contributes importantly to (a) screening for organic disease (b) monitoring of the response to treatment of inflammation and infection and (c) detection of inter current infection in immune compromised individuals and in the few specific diseases characterized by modest or absent acute-phase responses.

CRP values can never be diagnostic on their own and can only be interpreted at the bedside in full knowledge of all other clinical and pathological results. However they can then contribute powerfully to management, just as universal recording of the patients' temperature, an equally nonspecific parameter, is of great clinical utility [19].

Ankle-Brachial Index (ABI), Coronary Artery Calcium (CAC), Carotid Intima-Media Thickness (CIMT) - these emerging risk factors will be discussed in the next section.

Putting it together

The cardiovascular diseases refer to diseases affecting medium and large size arteries predominantly as a result of atherosclerosis which contributes to significant morbidity and mortality worldwide.

My hypothesis is that cardiovascular disease is triggered by chronic psychosocial stress.

As described in earlier section the term stress has changed its meaning from that of a non-specific body response to a 'monitoring system of internal and external cues', that is a modality of reactions of the mammalian central nervous system (CNS) which is critical to the adaptation of the organism to its environment. Most stressors are psychosocial and they set the stage for stress response. Cognitive appraisal mechanism determines affect (felt emotion). Once appraisal is made efferent impulses project to highly sensitive emotional anatomy in the limbic system especially in hippocampus to trigger visceral effector mechanism. This results in activation of Hypothalamus -pituitary - adrenal axis and sympathetic -adrenal - medullary axis.

Stress hormones and other mediators such as neuro transmitters, cytokines, and other hormones are essential for adaptation to challenges of daily life as well as major life stressors. This process has been called "allostasis", that is maintaining homeostasis or stability through change. When mediators of allostasis like cortisol and adrenaline are released in response to stressors or to life style factors

such as diet, sleep and exercise they promote adaptation and survival and are generally beneficial.

Chronic stress can promote and exacerbate pathophysiology through the same systems that are dysregulated. Chronic activation of the stress response which includes Hypothalamus -Pituitary-Adrenal (HPA) axis and Sympathetic-Adrenal -Medullary (SAM) axis results in chronic production of glucocorticoids and catecholamines (Figure 1). This results in systemic inflammatory process similar to the response initiated by pathogens or physical stressors. In anticipation of increased metabolic demands there is excess liberation of free fatty acids from adipose tissue into the circulation. The liver responds to free fatty acid influx by increasing low density lipoprotein production and cholesterol ester synthesis. There is activation of micro vascular circulation and endothelial dysfunction, as a result of innate immunity triggered by stress response.

This is the important junction which connects stress with pathophysiology of cardiovascular diseases developing as a result of process of atherosclerosis. We have extensively studied the pathophysiology of stress as above which results in systemic inflammation. The atherosclerosis develops as a result of immuno-inflammation. The pathogenesis of atherosclerosis begins with endothelial dysfunction which precedes atherosclerosis. The missing link is what causes atherosclerosis? The systemic inflammatory state enclosed in the pathophysiology of stress, drives the process from here on and the continuous LDL-C particles pour through "leaky endothelial cells" in the vessel walls. From here on the atherosclerosis is well studied and how it contributes to cardiovascular diseases.

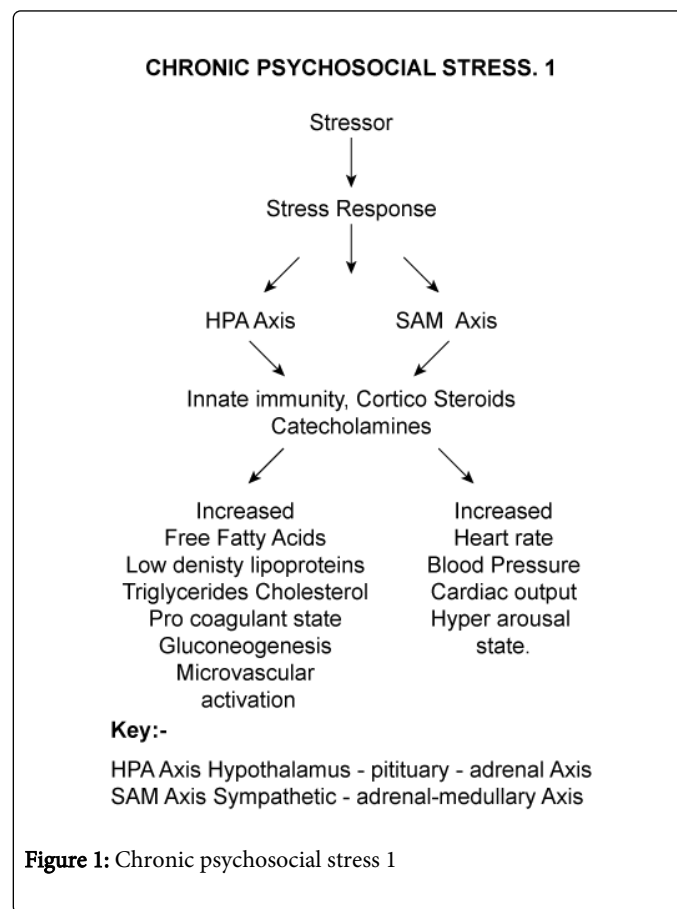
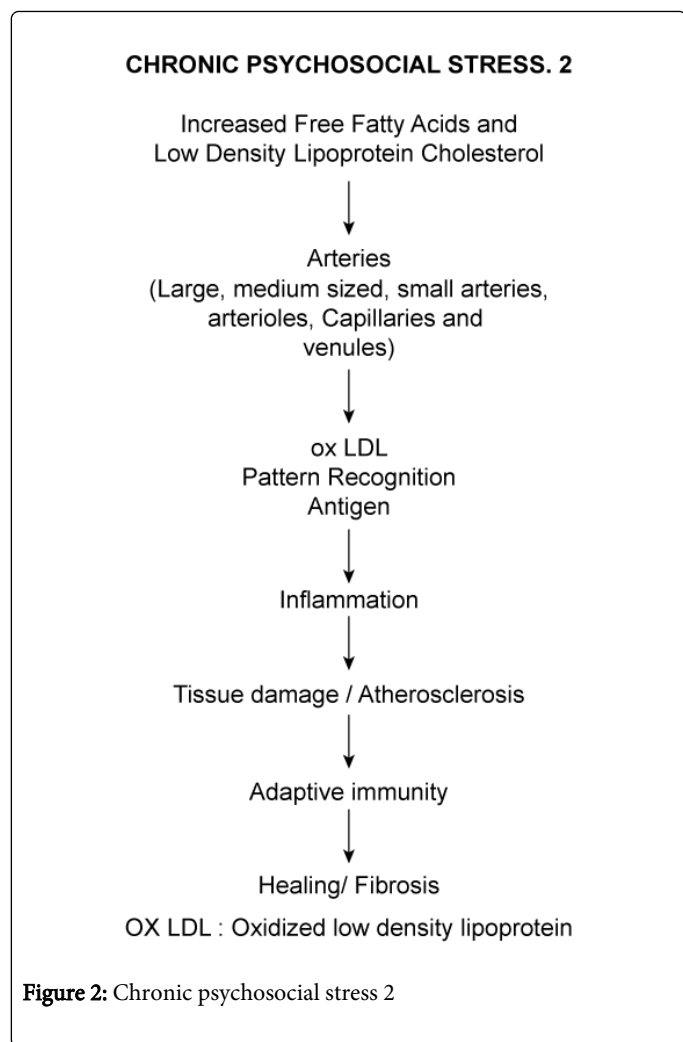


Figure 1: Chronic psychosocial stress 1



This activation of microvasculature results in increased transport of lipoprotein LDL-C across the endothelial cells which have increased permeability. In this situation it is dysregulated response to psychosocial stress. The nature of psychophysiological stress response is that of apparent preparatory arousal-arousal in preparation of physical exercise, when used in such a way, it is easy to see the adaptive utility of the stress response. Yet stress arousal in modern times under circumstances of strictly psychosocial stimulation might be viewed as inappropriate arousal of primitive survival mechanism, in that the organism is aroused for physical activity but seldom is such activity truly warranted and therefore, seldom does it follow [2]. The inflammatory cascade ensues in anticipation of increased metabolic demand. Free Fatty acids are mobilized continuously. The body utilizes the energy from fatty acids released from small fraction of LDL but the continuous high supply of LDL-C exceeds the bodies mechanisms to manage LDL-C by Nitrogen synthase and reverse transport by HDL-C. The excess LDL-C is transformed into oxidized LDL. These oxidized LDL particles are retained which are now cytotoxic, pro inflammatory, chemotactic and pathogenic. Oxidized LDL particles are antigenic and trigger inflammation activating innate immunity. There is mobilization of circulating monocytes across the endothelium which transform into macrophages and internalize oxidized LDL particles. These lipid loaded cells are called foam cells. Oxidized LDL particles go through pattern recognition process and

adaptive immunity is activated. There is release of cytokines, tumor necrosis factor alpha and IL -6, which results in production of C - reactive protein from hepatocytes. The inflammation caused by oxidized LDL is accompanied by oxidative stress and healing process results in tissue damage. This is seen in its various stages in medium and large vessels as atherosclerosis, while similar process is ongoing systemically. All the microvasculature is exposed to these changes and lipids are transported across the endothelium into the vessel walls, causing damage to body tissues i.e. pancreatic cells, renal parenchymal cells, brain such as leukoaraiosis, thyroid cells and so on (Figure 2).

Tip of the iceberg

The detailed literature review of pathogenesis of cardiovascular diseases, which according to my hypothesis, are initiated as a result of chronic psychosocial stress causing systemic inflammation and involve medium and large size arteries with a process of atherosclerosis, became the basis of generating my second hypothesis that the phenomenon of systemic inflammation involves the entire micro vascular circulation, resulting in processes similar to atherosclerosis in the small vessels, arterioles, capillaries and veins, involving tissues and organs sub served by those micro vascular beds and causing progressive damage and loss of function (Figure 2).

At this point I would review the current literature on microcirculation.

The microcirculation is highly responsive to and a vital participant in the inflammatory response. All the segments of the microcirculation (arterioles, capillaries and venules) exhibit characteristic phenotypic changes during inflammation that appear to be directed toward enhancing the delivery of inflammatory cells to the injured / infected tissue, isolating the region from healthy tissue and the systemic circulation and setting the stage for tissue repair and regeneration. The best characterized responses of the microcirculation to inflammation include impaired vasomotor function, reduced capillary permeability, and an increase in the rate of proliferation of blood and lymphatic vessels. A variety of cells that normally circulate in blood ie leukocytes, platelets or reside within the vessel wall (endothelial cells, pericytes) or in the perivascular space (mast cells), macrophages) are activated in response to inflammation. The activation products and chemical mediators released from the cells act through different well-characterized signaling pathways to induce the phenotypic changes in micro vessel function that accompany inflammation.

Inflammation is typically viewed as a localized protective response to tissue damage and / or microbial invasion, which serves to isolate and destroy the injuring agent and the injured tissue and prepare the tissue for eventual repair and healing. The survival value of the inflammatory response for both the injured tissue and the animal as a whole is an important physiological process. In most instances an inflammatory reaction is short lived and results in the desired protective response. However in some cases excessive and /or prolonged inflammation can lead to extreme tissue damage, organ dysfunction and mortality. The critical role of inflammation in diseases as diverse as atherosclerosis, diabetes, cancer, reperfusion injury and Alzheimer's disease accounts for the massive research efforts that have been directed toward understanding the mechanisms that initiate and regulate the inflammatory response.

The microcirculation plays a major role in the genesis and perpetuation of an inflammatory response. The microvasculature undergoes a variety of functional and structural changes during inflammation. These include a diminished capacity of arterioles to

dilate, impaired capillary perfusion, the adhesion of leukocytes and platelets in venules, enhanced coagulation and thrombogenesis, an increased vascular permeability to water and plasma proteins and an eventual increase in the rate of proliferation of blood vessels and lymphatic vessels. The net effect of responses are to (1) promote the delivery of inflammatory cells to the injured / infected tissue (2) dilute the injurious / inciting agents in the affected region, (3) isolate this region from healthy tissue and systemic circulation, and (4) set the stage for the regenerative process. The functional changes are evident during the acute phase of the inflammatory process ie, within minutes to hours after initiation of the response. The structural alterations on the other hand are manifested during chronic phase of the inflammatory response ie, days after the initial inflammatory insult. These temporal distinctions between the early and delayed micro vascular responses to inflammation are not synonymous with acute versus chronic inflammatory conditions, where the former is short lived self-resolving response that occurs over a period of hours to days, while the latter occurs over a period of weeks to years due to a persistent inflammatory stimulus. While the relative contribution of different cellular and humoral mediators may differ between acute and chronic inflammation, the role of the microvasculature in mounting and sustaining the inflammatory response is largely the same under the two conditions.

All segments of the vascular tree ie arterioles, capillaries and venules are affected by and contribute to the inflammatory response. The activation of endothelial cells (ECs) in each vascular segment by bacterial products and / or locally released mediators allow for a deliberate and coordinated response of the microcirculation to the inflammatory insult. Other components of the vascular wall including vascular smooth muscle (VSM) and pericytes, as well as cells that normally reside in the immediate perivascular region, such as mast cells and macrophages, all contribute to the inflammatory response and serve to induce and / or amplify the events associated with endothelial cell activation. Further amplification and perpetuation of the response results from the recruitment and activation of leukocytes and platelets, which bring their own armamentarium of releasable mediators into the inflamed vasculature [20].

I will now describe some of the diseases which are caused as a result of systemic inflammation initiated through psychosocial stress, triggering stress response.

Hypertension

The role of oxidative stress

Primary hypertension/essential hypertension accounts for 90% of all cases of hypertension. Increased sympathetic activity contributes due to activation of stress response among other factors. Oxidative stress results of excessive generation of reactive oxygen species (ROS) has a key role in the pathogenesis of hypertension. The modulation of the vasomotor system initiates ROS as mediators of vasoconstriction induced by angiotensin 11, endothelin 1 and urotensin 11 among others. Bioavailability of NO major vasodilator is highly dependent in the redox state.

Under physiological condition low concentration of intracellular ROS have an important role in the redox signaling monitoring vascular function and integrity.

Under pathological conditions increased level of ROS contributes to vascular dysfunction and remodeling through oxidative damage. In

human hypertension increase in the production of superoxide anions and hydrogen peroxide, a decrease in NO synthase and a reduction in antioxidant availability have been observed.

Hypertension is considered as most important risk factor for cardiovascular diseases. As discussed earlier the stress response generates systemic inflammation, hypertension results due to oxidized LDL particles causing oxidative stress and shares the common mechanism as macro vasculature developing atherosclerosis and CVD. Hypertension is manifestation of same pathological process rather than a risk factor.

The concept of target organ damage i.e. hypertensive retinopathy, heart disease and CKD due to hypertension also needs to be reconsidered as all of those tissues and organs develop inflammation and tissue damage due to common shared mechanism of systemic inflammation as a result of oxidative stress [21].

Diabetes mellitus

The current literature supports the role of oxidative stress in vascular disease in Diabetes.

The diabetes is associated with macro vascular manifestations which include atherosclerosis and medial calcification. The micro vascular consequences, retinopathy and nephropathy are major causes of blindness and end stage renal disease. The pathophysiology of vascular disease in Diabetes involves abnormalities in endothelial, vascular smooth muscle cells and platelet function. The metabolic abnormalities, hyperglycemia, increased free fatty acids and insulin resistance each provoke mechanisms that contribute to vascular dysfunction. These include decreased bioavailability of NO, increased oxidative stress, disturbance of intracellular signal transduction and activation of receptors for AGEs. In addition platelet function is abnormal and there is increased production of several prothrombotic factors. The abnormalities contribute to the cellular events that cause atherosclerosis and increased risk of cardiovascular disease events that occur in patients with Diabetes and atherosclerosis [22].

There is increasing evidence that an ongoing cytokines-induced acute phase response (sometimes called low grade inflammation), but part of wide spread activation of the innate immune system) is closely involved in the pathogenesis of type 2 Diabetes and associated complications such as dyslipidemia and atherosclerosis. Elevated circulating inflammatory markers such as c- Reactive protein and interleukin -6 predict the development of type 2 Diabetes and several anti-inflammatory proteins lower both acute phase reactions and glycemia. (Aspirin and Thiazolidinediones) and possibly decreases the risk of developing type 2 Diabetes (statins). Among the risk factors for type 2 Diabetes which are also known to be associated with activated innate immunity are age, inactivity, certain dietary components, smoking psychosocial stress and low birth weight. Activated immunity may be the common antecedent of both type 2 Diabetes and atherosclerosis, which probably develop in parallel. Other features of type 2 Diabetes such as fatigue, sleep disturbance and depression are likely to be at least partly due to hypercytokinemia and activated innate immunity.

There has been a recent explosion of interest in the notion that chronic low grade infection and activation of the innate immune system are closely involved in the pathogenesis of type 2 Diabetes. For example since this hypothesis was first proposed in 1997 and 1998 at least 12 studies have shown that circulating markers of inflammation acute phase reactants or interleukin -6 (IL)-6, (the major cytokine

mediator of the acute phase response) are strong predictors of the development of type 2 Diabetes [23].

In UK Prospective study of Type 2 Diabetes long term increase in fasting plasma glucose was accompanied by progressive decline in Beta cell function of pancreas and 4% /year (UK Prospective Diabetes Study Group 1995) By the time of diagnosis mean Beta cell function was < 50% and further deterioration of Beta cell function was not prevented by any of the diabetic therapies used in the study.

Observed rate of Beta cell destruction suggest loss of Beta cell function begins around 12 years prior to diagnosis (Holman, 1998). This explains why patients require escalation in the number and dosage of hypoglycemic agents with time and eventually become refractory to oral treatment, requiring Insulin [24].

Diabetes is considered as a major risk factor for CVD which increases the mortality 3-4 fold. Reviewing the literature it appears that Diabetes develops due to same pathophysiology as a result of systemic inflammation from stress response generated by chronic psychosocial stress, activating innate immunity, resulting in activation of microcirculation, increased oxidized LDL particles, which result in oxidative stress and damage the pancreatic beta cells. This results in tissue damage and Diabetes hence this is the result of micro vascular disease. The other complications such as retinopathy, neuropathy and kidney disease are due to systemic nature of the inflammatory process. macro vascular disease as discussed develops in parallel due to same pathology. Hyperglycemia adds to metabolic burden of course. Recent prospective clinical trial shows that normalization of glycemia failed to reduce cardio vascular burden in the diabetic population.

The Diabetes is one of the several organs affected by the systemic process of inflammation rather than a risk factor.

Ageing

Ageing has come out as an important risk factor for CVD.

As reviewed in earlier section ageing phenomenon is the result of mild chronic allostatic load and is due to micro vascular circulation disease.

The article published in American physiological society states, "You're as old as your arteries" describes, Endothelial dysfunction develops with age increases the risk of age associated vascular disorders. Nitric oxide insufficiency, oxidative stress and chronic low grade inflammation induced by up regulation of adverse cellular signaling processes and imbalances in stress resistance pathways, mediate endothelial dysfunction with ageing. Healthy life style behaviors preserve endothelial function with ageing by inhibiting these mechanisms [25].

In the light of the above there is ongoing low grade inflammation as a result of mild allostasis which results in peace meal necrosis due to inflammation / healing process in every tissue and organ of the body sub served by microcirculation and macrocirclation from oxidative stress by oxidized LDL particles.

This results in diabetes, hypertension, CVD, Alzheimer's disease, chronic kidney disease, cataracts, arthritis, Atrial fibrillation, left ventricular systolic dysfunction, conduction system fibrosis and heart blocks, skeletal muscle atrophy, connective tissue loss, osteoporosis and so on.

Ageing may be considered as a risk factor for CVD, Diabetes and hypertension, as the stress response due to psychosocial stress gets amplified due to increased allostasis faced with ageing.

Obesity

Obesity is a principal causative factor in the development of metabolic syndrome. Increased oxidative stress in accumulated fat is an important pathogenic mechanism of obesity associated metabolic syndrome. Fat accumulation correlated with systemic oxidative stress in humans and mice.

Oxidative stress in diabetes impairs glucose uptake in muscle and fat and decreases insulin secretion from pancreatic beta cells. Increased oxidative stress underlies pathophysiology of hypertension and atherosclerosis by directly affecting vascular wall cells [26].

Obesity therefore is not a risk factor but one of the several organs which become affected due to micro vascular circulation disease.

Metabolic Syndrome

High level of free radicles together with low anti-oxidant capacity detected in obese adults indicate elevated oxidative stress which is – together with systemic inflammation – further potentiated in the case of obese patients with metabolic syndrome. This imbalance in oxidative /antioxidative state and subclinical inflammatory state leads to higher risk of atherosclerosis and diabetic complications.

Met S which is considered as a risk factor for CVD is a constellation of risk factors which has already discussed, i.e. hypertension, diabetes and obesity are the result of micro vascular disease initiated by activation of innate immunity triggered by stress response. Met S therefore is a manifestation of involvement of all those tissues in the inflammatory response and developing oxidative stress from oxidized LDL particles causing tissue damage. There are all the other features of inflammation i.e. markers of acute phase response and procoagulant state [27].

Met S demonstrates that all of these conditions share a common mechanism working from one triggering source.

Chronic kidney disease

The prevalence of CKD in the US adult population was 11% (19.2 million) using standardized criteria based on estimated GFR and persistent albuminuria (by NHANES 111) [28].

Aside from hypertension or diabetes, age is a key predictor of CKD and 11% of individuals older than 65 years without hypertension / or diabetes had stage 3 or more CKD.

Sympathetic hyperactivity in CKD

Cardiovascular morbidity and mortality importantly influence life expectancy of patients with CKD. Traditional risk factors are usually present but several other factors have been identified. CKD is often characterized by an activated sympathetic –renin system. This may contribute to pathogenesis of renal hypertension but it may affect adversely prognosis independent of its effect on blood pressure.

Hypertension is common in patients with CKD. Prevalence varies between 30 -100% depending on target population, cause of renal disease and level of renal function. Hypertension has been viewed as volume dependent. CKD is often characterized by an activated sympathetic nervous system.

Sympathetic nervous system is a part of autonomic nervous system. Its activity can be derived indirectly from sympathetic effector response. i.e. blood pressure or heart rate. Nor-epinephrine in plasma is net result of discharge, reuptake, metabolism and clearance, not suitable for accurate measure of the disease. Sleep apnea associated with sympathetic hyperactivity. LVH is related to increased sympathetic activity. Increased sympathetic activity is associated with Congestive heart failure, arrhythmias and atherosclerosis in experimental animals [29].

Role of oxidative stress and antioxidant therapy

Oxidative stress is frequently associated with and is partly involved in the pathogenesis of chronic renal failure, hypertension and their complications.

The up regulation of nicotinamide adenosine dinucleotide phosphate (reduced form) oxidase and tubulo-interstitial accumulation of activated T cells, macrophages and superoxide producing cells are partly responsible for oxidative stress in several models of hypertension. Antioxidant therapy alleviates hypertension, averts nuclear factor kappa B activation and mitigates tubulo-interstitial inflammation in hypertensive animals.

Oxidative stress contributes to hypertension, endothelial dysfunction and brain disorder in chronic renal failure and down regulation of superoxide dismutase and up regulation of nicotinamide adenosine dinucleotide phosphate (reduced form) [30].

CKD is considered as a complication of hypertension and diabetes. CVD is strongly associated with CKD. The pathophysiology as described in above articles highlights role of increased sympathetic activity and oxidative stress which are also important in CVD, hypertension and diabetes. The weight of the evidence suggests that CKD develops in parallel with these conditions sharing the common mechanism of micro vascular disease from activated innate immune response triggered by HPA and SAM axes from stress. There is gradual loss of renal parenchyma by repeated episodes and / or chronic inflammation and healing with fibrosis from oxidative stress resulting from oxidized LDL ultimately requiring replacement therapy with dialysis.

Psychiatric disorders

Depression, Chronic anxiety disorders and Schizophrenia

Increasingly physical disorders such as obesity, hypertension and type 2 Diabetes are being recognized as significant co morbidities in people with severe mental illnesses, including psychotic disorders such as Schizophrenia. Whether these disorders are part of the disease process itself through increased stress and inflammatory responses, genetic vulnerabilities or environmental factors versus sequel of the treatment of the disease, has been a matter of debate.

Recent evidence has suggested that HPA axis- dysregulation – also may play a significant role in the development of various components of the Met S. While increased cortisol production is a normal response in acute stress, several studies have demonstrated a disruption in normal HPA axis activity and relative hypercortisolemia in patients with schizophrenia. Ryan and colleagues have recently shown that first- episode treatment – naïve patients with schizophrenia demonstrated a significantly higher plasma cortisol level along with higher percentage of patients having impaired fasting glucose,

increased fasting glucose and increased insulin resistance compared with matched control group [31].

Clinical depression and influencing risk markers of coronary heart disease

The study examined the relation between depression and the expression of inflammatory risk markers implicated in the pathogenesis of coronary heart disease. One hundred adults were enrolled.. Fifty subjects met the diagnostic criteria for clinical depression. The remaining were demographically matched controls with no history of psychiatric illness. The depressed subjects exhibited significantly higher levels of the inflammatory marker C-reactive protein and interleukin -6 compared with control subjects. These findings indicate that in otherwise healthy adults depression is associated with heightened expression of inflammatory markers implicated in pathogenesis of coronary heart disease [32].

A review of the literature revealed high comorbidity of chronic obstructive airway disease (COPD) and states of anxiety and depression, indicative of excess, psychiatric morbidity in COPD.

The existing stand point to a prevalence of clinically significant symptoms of depression and anxiety amount to around 50%. The prevalence of panic disorder and major depression in COPD patients is correspondingly markedly increased compared to general population. Pathogenic mechanisms remain unclear but both psychological and organic factors seem to play a role. The clinical and social implications are severe and the concurrent psychiatric disease may lead to increased morbidity and mortality to improve quality of life [33].

The prevalence of type 2 Diabetes is increased in patients with schizophrenia compared with general population. Holt et al, 2004. Although many factors, including genetic and life style issues contribute to this association, there has been a recent surge in interest in the subject because of the possible link between the use of atypical anti-psychotic drugs and the development of diabetes.

The analysis of the current literature strongly points towards the concept that psychiatric disorders depression, chronic anxiety, schizophrenia and psychosis share the same pathophysiology as other conditions such as coronary heart disease, hypertension, diabetes, metabolic syndrome, obesity and chronic obstructive pulmonary disease and develop as a result of micro vascular disease affecting the regions of the brain ie limbic structure, hippocampus, medial prefrontal cortex and amygdala. The studies have demonstrated increased inflammatory markers. It appears that the brain tissue has high level of receptors for corticosteroids. There is inflammation and healing and oxidative stress resulting in dysfunction causing various psychiatric disorders as described above. There is also evidence of cortical atrophy.

Nonalcoholic fatty liver disease

Although the epidemic of obesity has been accompanied by an increase in the prevalence of the metabolic syndrome, not all obese develop the syndrome even lean individuals can be insulin resistant. Both lean and obese insulin resistant individuals have an excess of fat in the liver which is not attributable to alcohol or other known causes of liver disease, a condition defined as Non Alcoholic Fatty Liver Disease (NAFLD) by gastroenterologist. The fatty liver is insulin resistant. Liver fat is highly significantly and linearly correlated with all components of the metabolic syndrome independent of obesity, over

production of glucose, VLDL, CRP and coagulation factors by the fatty liver could contribute to the excess risk of cardiovascular disease associated with the metabolic syndrome and NAFLD. Both of the later conditions also increase the risk of type 2 diabetes and advanced liver disease. The reason why some deposit fat in the liver where as others do not is poorly understood. Individuals with fatty liver are more likely to have excess abdominal fat and inflammatory changes in adipose tissue. Intervention studies have shown that liver fat can be decreased by weight loss, PPAR γ agonists and insulin therapy [34].

NAFLD by its association with metabolic syndrome shares the same features of inflammatory state i.e. over production of glucose, insulin resistance, increased lipids, coagulation factors and CRP as in activated immunity as a result of stress response, triggering HPA axis and points towards micro vascular disease affecting the liver.

Inflammatory bowel disease

Chron's Disease (CD) and Ulcerative Colitis (UC) known as Inflammatory Bowel Disease (IBD) are fairly common chronic inflammatory conditions of the gastro intestinal tract. Although the exact etiology of IBD remains unclear dysfunctional immune regulation of the gut is believed to be the main culprit. Amongst the immune regulatory factors, reactive oxygen species are produced in abnormally high levels in IBD. Their destructive effects may contribute to the initiation and / or propagation of the disease. It is generally believed that IBD is caused by gasro intestinal tract immune dysregulation because the disease is accompanied by a considerable inflammatory cells in gut mucosa. Oxidative stress is a potential etiological and / or triggering factor of IBD, because the detrimental effects of reactive oxygen molecules (ROI) have been well established in the inflammatory process [35].

Osteoarthritis

Review

Physiology and pathophysiology of nitrosative and oxidative stress in osteoarthritic joint destruction.

Osteoarthritis is one of the most common chronic disease with increasing importance due to increased life expectancy. An imbalance between the free radical burden and cellular scavenging mechanisms defined as oxidative stress have been identified as a relevant factor in OA pathogenesis [36].

Allergic Rhinitis

Oxidative and anti-oxidant factors in pathophysiology of allergic rhinitis.

Conclusion

Our results suggest that imbalance between oxidative and anti-oxidant defense mechanisms play a role in the etiopathogenesis of allergic rhinitis [37].

Bronchial Asthma

Airway inflammation is the most prominent cause of the recurrent episodes of airflow limitation in asthma. Recent research has revealed that numerous biologically active pro inflammatory mediators are responsible for the pathogenesis of asthma. Among these mediators, there is increasing evidence that endogenous or exogenous Reactive

Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are responsible for the airway inflammation of asthma. Many reports have shown that there is an excessive production of ROS and RNS in the airways of asthmatic individuals compared with healthy subjects. Excessively produced ROS and RNS have been reported to lead to airway inflammation, airway hyper responsiveness airway micro vascular hyper permeability, tissue injury and remodeling in animal models and human studies. Although human lungs have a potent anti-oxidant system, excessive oxidative and nitrate stress leads to an imbalance of oxidant / antioxidant [38,39].

Oxidative stress in chronic obstructive airway disease (COPD)

Oxidative stress is now recognized as a major predisposing factor in the pathogenesis of COPD. Existing therapies for COPD are ineffective at halting disease progression, with bronchodilators being the mainstay of pharmacotherapy providing symptomatic relief only. Antioxidant capacity in COPD is substantially reduced as a result of cigarette smoking / or exacerbation, due to the continued production of ROS from endogenous sources.

Conclusion

Elevated levels of reactive oxygen species and carbonyls are found in COPD and this may be associated with increased inflammation, airway remodeling, auto immunity and corticoid resistance. In addition systemic oxidative stress may also be a causal link in many COPD comorbidities such as cardio vascular diseases and metabolic syndrome. Local oxidative stress may also promote the development of cancer [39].

Atrial Fibrillation

There is growing evidence that oxidative stress is involved in the pathogenesis of atrial fibrillation. Many known triggers of oxidative stress such as age, diabetes, smoking, inflammation and renin angiotensin 11 signaling activation are linked with an increased risk of the arrhythmia. Blocking angiotensin 11 signaling and other drugs with anti-oxidant properties can reduce the incidence of atrial fibrillation. Now studies in animal models and human tissue, have shown directly that atrial fibrillation is associated with increased atrial oxidative stress. We review the evidence for a role of oxidative stress in causing atrial fibrillation and propose a unifying hypothesis that multiple triggers elicit oxidative stress which acts to enhance the risk of atrial fibrillation through ion channel dysregulation [40].

Atrial Fibrillation (AF) may persist due to structural changes in the atria that are promoted by inflammation. C Reactive Protein (CRP) a marker of systemic infection, predicts cardiovascular events and stroke a common sequel of AF.

Conclusion

CRP is elevated in AF patients. This study is the first to document elevated CRP in non -post operative arrhythmia patients. These findings are reinforced by stepwise CRP elevation s with higher CRP burden. Although the cause of elevated CRP levels in AF patients remains unknown, elevated CRP may reflect an inflammatory state that promotes persistence of AF [41].

Statin therapy lowers the risk of new onset atrial Fibrillation in patients with end stage renal disease.

In Statin group the incidence of developing atrial fibrillation was significantly lower than in cohort group (1.1% vs 3.8%, $P < 0.001$).

- The PS based selection process identified 2146 patients receiving statin and 2146 who did not receive statin.
- The incidence of developing atrial fibrillation remained lower in statin group than that in cohort group 2.4% vs 4.9% ($P < 0.001$).
- After PS matching cox,s proportional hazard regression analysis showed that there was a protective effect of developing atrial fibrillation in a dose dependent manner.
- The protective effect was more obvious in subjects with younger age, female gender, hyperlipidemia, coronary artery disease and peripheral artery disease, in subjects without taking angiotensin converting enzyme inhibitor and angiotensin receptor blocker [42].

Oxidative stress and vascular disease

Oxidative stress is associated with several cardiovascular diseases including atherosclerosis, hypertension, congestive heart failure and diabetes. Oxidation of LDL plays a key role in pathogenesis of atherosclerosis.

Oxidative stress plays a key role in endothelial dysfunction associated in these diseases as superoxide O_2^- inactivates nitric oxide (NO) and thereby produce endothelial dysfunction. Endothelial dysfunction is associated with and may contribute to an increased risk of cardiovascular events.

Aortic valvular stenosis / Degenerative calcific aortic stenosis. Non rheumatic tricuspid aortic valve stenosis has many of the morphological characteristics of atherosclerosis including lipid deposition, inflammation and calcification. Risk factors are similar for aortic stenosis, atherosclerosis hypercholesterolemia, male gender and smoking, suggesting that pathophysiology of aortic valvular stenosis and atherosclerosis may be similar.

The author postulates that superoxide may play a role in pathophysiology of “degenerative calcific aortic stenosis” [43].

Oxidative stress in cataracts

Oxidative stress is the result of an imbalance of antioxidants and oxidants.

Since toxic free radicals are the result of normal metabolism, there destruction is imperative. Cataracts are the leading cause of blindness worldwide. Opacity of lens is a direct result of oxidative stress. Cataracts occur primarily due to age but also are common in diabetes where superoxide in the mitochondria is elevated as a result of hyperglycemia [44].

Oxidative stress and cancer

In aerobic life oxidative stress arises from both endogenous and exogenous sources. Despite antioxidant defense mechanisms, cell damage from oxygen free radicles (OFR) is ubiquitous. OFR- related lesions that do not cause cell death can stimulate the development of cancer. A large body of evidence suggests important role of OFR in the expansion of tumor clones and the acquisition of malignant properties. In view of these facts OFR may be considered as an important class of carcinogens. Therefore the ineffectiveness of preventive antioxidant treatments as documented in several clinical trials, is surprising. However the difficulties of antioxidant

interventions are explained by the complexity of both free radical chemistry and cancer development. Thus reducing the avoidable endogenous and exogenous cause of oxidative stress is for the present the safest option [45].

Oxidative stress

As oxidative stress has been observed in several diseases of macro vascular and micro vascular origin, it will be important to determine its significance in these disease processes.

Oxidative stress has been described in earlier section under endothelial dysfunction.

Oxidative stress is defined as imbalanced redox state in which pro – oxidants overwhelm anti-oxidant capacity, resulting in increased production of Reactive Oxygen Species (ROS).

This review summarizes the results and discussion of an UNESCO-MCBN supported symposium on oxidative stress and its role in the onset and progression of diabetes mellitus. There is convincing evidence that the generation of Reactive Oxygen Species (ROS) is increased in both types of DM and that the onset of DM is closely associated with oxidative stress.

One major hypothesis is that oxidized lipoprotein (ox LDL) contributes to the cardiovascular complications of diabetes. Several studies have demonstrated increased LDL oxidation in diabetic patients when compared to their corresponding controls. The concept of imbalance between oxidative stress measures and antioxidant depletion has been applied to pro-atherogenic LDL oxidation process in diabetic patients. Leonhardt reported an imbalance between elevated ox LDL levels and decreased RRR-alpha-tocopherol levels. (Cholesterol standardized) in the LDL particles of diabetes when compared to healthy controls. The increase in LDL modification by oxidation may therefore not only correlate with increased levels of ROS but also with the decreased antioxidant protection. A decrease in antioxidant capacity has been observed in the plasma of diabetic patients by several research groups [46].

Ox LDL plays a central pathogenic role in the arterial wall. Various known risk factors for atherosclerosis lead to a state of oxidative stress characterized by excessive production of ROS that is not neutralized by the body, s antioxidant defense. Kita et al. have shown the athero - protective effects of the antioxidant Probuco in Watanabe Heritable Hyperlipidemic (WHHL) rabbits as it limited oxidation of LDL and prevented foam cell formation. This work established the significance of ox LDL in atherosclerosis. Now it is well known that ox LDL induced pro -oxidant state is present in all stages of atherosclerosis from the beginning to the acute thrombotic event. ox LDL inhibits the expression of the constitutive endothelial enzyme Nitric Oxide Synthase (eNOS), which inhibits a number of steps involved in atherogenesis. In addition it results in generation of ROS from endothelial cells, vascular smooth muscle cells and macrophages. Release of ROS also includes expression of adhesion molecules on endothelial cells, proliferation of macrophages, stimulates collagen formation in fibroblasts, leads to proliferation and migration of vascular smooth muscle cells and activation of platelets [47].

Oxidative stress is produced during the process of inflammation initiated by ox LDL particles in which several additional ROS are released resulting in tissue damage already caused by ox LDL. Oxidative stress therefore is the ultimate consequence of this inflammatory process.

Presence of an antioxidant imbalance in human tissues

In reaction to mild oxidative stress, tissues often respond by producing more antioxidants, however severe oxidative stress depletes body's antioxidant resources and overtake its ability to produce more antioxidants, which leads to lower antioxidant levels. Therefore interpretation of antioxidant concentration without knowing the states of ROS and course of the disease would be biased.

Summary

Diseases of macro vascular and micro vascular circulation have strong association with chronic psychosocial stress in their initial presentation and recurrent episodes. There is increased sympathetic activity and elevated levels of serum cortisol supporting activation of HPA and SAM axes, presence of increased inflammatory markers such as CRP, interleukin -6, tumor necrosis factor alpha consistent with systemic inflammation and dyslipidemias with ox LDL formation resulting in oxidative stress, causing atherosclerosis and tissue damage in territories of macro vascular and micro vascular circulation. As these conditions share several common features and present as multiple co morbidities in an individual, it supports the hypotheses that these disorders manifest in parallel, having a common pathophysiological mechanism, which is chronic psychosocial stress.

Discussion

The role of chronic psychosocial stress in pathophysiology of cardiovascular diseases has been presented as a first hypothesis. The second hypothesis is derived in which same pathophysiologic processes are implicated in the development of several diseases as a result of micro vascular circulation involvement.

Once chronic psychosocial stress sets in chronic inflammation which is global in reach, the question arises why is the inflammation not present in every tissue with same severity. This has been observed in macro vascular diseases that, some arterial segments are more susceptible than others and some organs are more susceptible than others in case of micro vascular diseases. This may be explained by the fact that some tissues may have very high concentration of receptors i.e. brain tissue, hypothalamus, hippocampus and amygdala and prefrontal cortex have very high concentration of corticosteroid receptors, similarly renal parenchyma has dense sympathetic innervation.

The stress response may be of variable severity depending on the level of stress an individual is exposed to and / or magnitude of appraisal.

Low level chronic stress generates mild stress response, low grade inflammation causing mild allostatic load as seen in ageing. Therefore in ageing low level chronic inflammation as a result of ox LDL particles causes slow piece meal tissue damage (Figure 3).

This results in increased incidence of hypertension, diabetes, chronic kidney disease, Alzheimer's disease, osteoporosis, osteoarthritis, coronary artery disease, atrial fibrillation, congestive heart failure from non-ischemic cardiomyopathy, cataracts and so on.

The chronic moderate level of psychosocial stress generates stress response of higher intensity resulting in accelerated systemic inflammation. There is increased delivery of lipoproteins including LDL across the inflamed, permeable endothelial cells to the macro and micro vascular circulation, which causes more rapid progression of

atherosclerosis and tissue damage in the organs affected. This results in more rapid progression of the diseases; hence there is progression of atherosclerosis in macro circulation and more tissue damage in micro vascular territories, resulting in progressive loss of function, more requirement of insulin in diabetes, more thyroxin replacement in thyroid disease and so on.

At this point if there is a change in the level of stress to higher intensity, a more robust stress response will be generated, resulting in amplification of HPA and SAM axes, which will result in rapidly progressive inflammation. This will in case of atherosclerosis in coronary arteries result in rapid expansion of soft plaque extending towards intima, rupture, increased procoagulant state, platelet activation, clinically causing acute coronary syndrome, which may progress to acute myocardial infarction. The adaptive immunity will take several days to begin its effect.

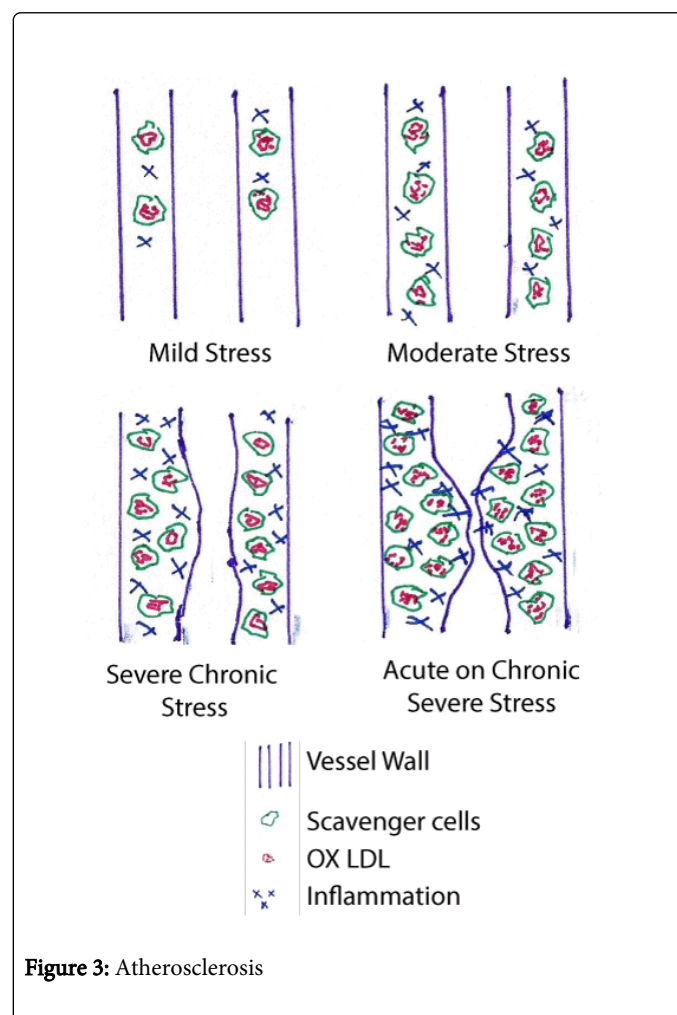


Figure 3: Atherosclerosis

In case of organs sub served by microcirculation i.e. pancreas, thyroid gland, kidney and brain tissues this may result in accelerated damage and loss of function.

Once adaptive immune response begins, the healing process starts, inflammation begins to resolve and fibrosis develops until the next episode of stress related relapse. In case of macro vascular disease due to focal disease and total occlusion, there will be loss of tissue in segmental manner such as myocardial infarction in territory of epicardial artery, stroke or peripheral arterial occlusion but in micro

vascular disease there can be extensive diffuse loss of tissue, resulting in serious consequences.

The study quoted in section of stress, published in American Journal of Psychiatry.

Emphasizes that individuals who are already suffering from major depression, which is a disease due to systemic inflammation from chronic stress, associated with elevated markers of inflammation (i.e. IL-6 performed in this case). Acute stress has resulted in mounting another stress response and amplifying the activation of HPA and SAM axes, triggering further inflammation (Figure 4).

Cardiovascular disease which is a common comorbid condition with clinical depression or without clinical depression will demonstrate a similar acute response on preexisting moderate atherosclerotic process which might have been clinically quiescent or stable. This may transform into acute coronary syndrome.

Most of the macro vascular diseases and micro vascular diseases lend themselves to diagnosis once clinically manifested and may be detected by routine testing as screening measures. Hence diabetes can be diagnosed by blood sugar assays, CKD by albuminuria and e GFR estimation, Thyroid disorders by thyroid function tests, Fatty liver by liver function test abnormalities and ultrasound, retinopathy and cataracts by eye exam, COPD by pulmonary function tests, Pulmonary hypertension by echocardiogram, systemic hypertension by clinical examination, coronary artery disease by stress testing, CAC and coronary angiography, and carotid disease by carotid ultrasound.

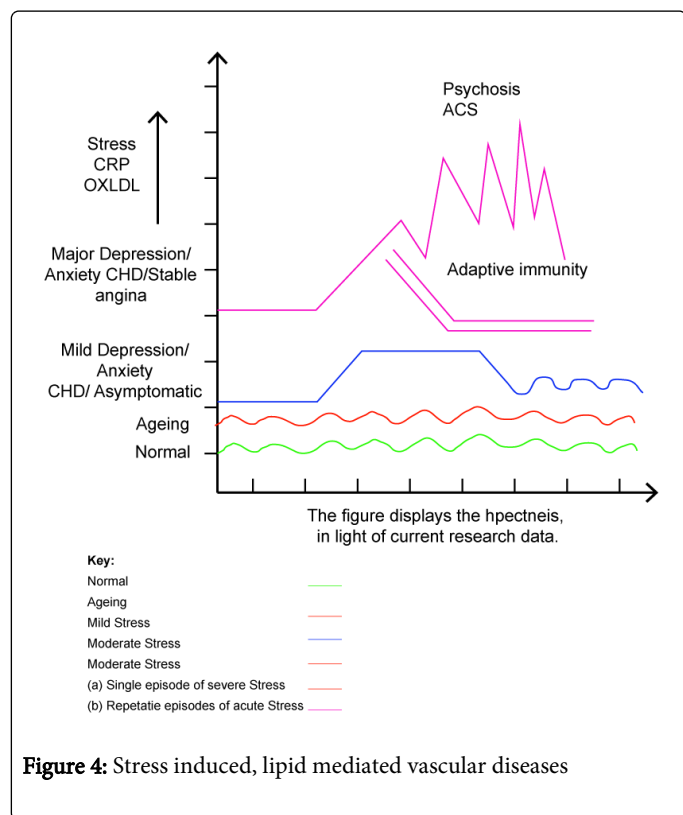


Figure 4: Stress induced, lipid mediated vascular diseases

If these tests are abnormal it indicates that disease process is already present and we are dealing with secondary prevention. The interventions initiated as a result have been focused largely on symptomatic management as seen in articles on COPD and diabetes presented in earlier sections and disease process continues to progress

until it reaches end stage with complete tissue damage. The same is the case in osteoarthritis and thyroid disorders. This eventually results in the need for replacement therapy, i.e. Thyroxin in thyroid disorder, dialysis /renal transplant in CKD, insulin in diabetes, Heart transplant in non-ischemic cardiomyopathy, liver transplant in advance liver disease from fatty liver and total hip and knee replacement in end stage osteoarthritis, and aortic valve replacement in aortic stenosis.

It is of more serious consequences in central nervous system diseases especially small vessel diseases such as Alzheimer disease, multiple sclerosis, Parkinson's disease, chronic anxiety disorders, depression and schizophrenia. These conditions do not lend themselves to objective laboratory evaluations, until they present clinically which result in less satisfactory outcomes as cortical necrosis may have already ensued.

It is important to outline ways to ensure primary prevention of all these diseases resulting from psychosocial stress.

As far as risk factors are concerned, most of the conventional risk factors are, indeed manifestation of various organs involvement presenting at different time frames in an individual i.e. diabetes and hypertension.

Hyperlipidemia / Dyslipidemia: LDL -C is the key player in the process of inflammation as seen in atherosclerosis. Although elevated serum levels signify increased risk of CVD the benefits of LDL lowering have been demonstrated in any range in Jupiter Trial for primary prevention and HPS (Heart Protection Study) for secondary prevention [48,49]. It is the influx of LDL particles on continuous basis across the endothelium into arterial wall which results in ox LDL formation and inflammation, irrespective of LDL levels in circulation.

Out of emerging risk factors CAC and CIMT are disease markers as these demonstrate the presence of disease process, which predicts future events and their presence can raise the concern for this process to be also present in other organs sub served by microcirculation. ABI reflects the severity of stenosis, as it predicts future events if < 1.1 or > 1.4 but does not have the ability to demonstrate a transition in increased biologic activity of the atherosclerotic process.

hs-CRP if elevated, reflects one of the steps in the inflammation process if no other etiologies are contributing to its elevation such as infection or cancer, provided there is no significant liver disease which will disqualify it from predicting the disease activity. It is a disease marker rather than a risk factor. It can predict the severity of inflammatory process by its rising levels, which may fall with resolution of inflammation. As seen CRP is not specific to cardiovascular diseases / macro vascular diseases but demonstrates this behavior in all the tissues undergoing inflammation as a result of psychosocial stress, ie pancreas in diabetes, renal parenchyma in CKD and thyroid inflammation in thyroid and in psychiatric diseases.

The definite modifiable risk factors are ageing, smoking, atherogenic diet / hyperlipidemia and physical inactivity.

Ageing has been discussed already. It has low grade inflammation, which accentuates the inflammation caused by chronic psychosocial stress.

As far as diet as a risk factor is concerned, atherogenic diet with high saturated fat is a risk factor for these vascular diseases. Body is continuously mobilizing free fatty acids due to chronic stress related systemic inflammation and dietary saturated fat keeps adding the fuel for ox LDL production in the arterial walls. Restricting dietary

saturated fat decreases this burden and hence contributes in decreasing the inflammation.

Decreased physical activity is a risk factor for CVDs. Promoting physical activity decreases the risk, most importantly by increase in fat metabolism with activity and exercise thereby decreasing LDL-C availability for conversion to ox LDL.

Cigarette smoking is a risk factor for CVDs. Nicotine is a strong activator of the HPA axis. Low grade inflammation and increased inflammatory markers such as interleukin-6 and CRP are associated with cigarette smoking [50]. As reviewed in earlier section the pathophysiology is similar in individuals with cigarette smoking on vasculature i.e. inflammation and atherosclerosis as seen in typical CVDs associated with dyslipidemias. Thus cigarette smoking accentuates the effects of inflammation by dyslipidemias in similar ways as ageing process.

Management

Primary prevention

The role of evaluation for psychosocial stress in each individual needs to be placed as an essential component of preventive medicine. Non atherogenic diet and exercise / increased physical activity should be promoted as a public health measure in every individual, smoking hazards should be explained, cessation of smoking encouraged and assisted in cessation efforts.

The role of laboratory markers such as hs-CRP may be ascertained. As it was observed in Jupiter Trial in 2008, that in apparently healthy individuals with low LDL-C (130 mg/dl) elevated hs-CRP>2 mg/dl, reductions in non-fatal, stroke and revascularization were observed among those randomized to statin therapy. The key finding of JUPITAR was the benefit of statin therapy for primary prevention among patients without elevations of LDL-C at baseline [48].

The age in this trial as inclusion criteria was > 50 years in men and > 60 years for women. The primary endpoints focused on macro vascular diseases.

It is important to establish the role of the hs-CRP starting at younger age, as oxidized LDL formation may proceed in arterial walls by their continuous entry through leaky endothelium in any range of LDL- C levels in blood where they are only passing through. This is relevant for diseases of micro vascular circulation as well due to increased incidence of diabetes and mental illnesses in younger age.

Role of Ox LDL levels in blood may be explored

3. Intervention with statin may be evaluated.
4. Role of anti-oxidants may be explored.
5. Role of centrally acting sympatholytic may need to be studied as an adjunct to other measures.

Secondary prevention

1. As psychosocial stress is the main factor in the development of these diseases, it is important to evaluate every individual with these diseases for psychosocial stress and assist in stress reducing techniques.

It may be necessary to determine if these individuals are more susceptible to stress than others. Contribution of genetic factors,

environmental conditions, maternal stress working in prenatal period or early life stress and adolescent challenges may operate for chronic stress.

Role of centrally acting anti-hypertensive agents may be revisited. They are reported to have blood pressure independent effects. Centrally acting agents and, in particular clonidine have a number of alternate uses beyond BP reduction. Clonidine may be used for migraine prophylaxis and post-traumatic stress syndrome both related to stress and micro vascular disease 51. In normotensive diabetic humans Moxonidine reduced albuminuria without affecting BP. Sympathetic hyperactivity in CKD can be reduced by several types of antihypertensive medicines. Both ACE inhibitors and angiotensin 11 antagonists can reduce but not normalize MSNA in chronic renal failure patients. Addition of a centrally acting sympatholytic agent Moxonidine to chronic treatment with an angiotensin 11 receptor antagonist normalizes blood pressure and MSNA [29].

2. Non atherogenic diet and increased physical activity is an integral part of the management.

3. Statin therapy.

Statin therapy should be instituted with high intensity therapy according to 2013 ACC /AHA Guidelines on the Treatment of Blood Cholesterol to reduce atherosclerotic cardiovascular risk in Adults. However the scope should be extended to disease of micro vascular circulation as well.

Diabetes may be discussed as a model. The ox LDL is the culprit, results in tissue damage from inflammation, while euglycemia is achieved with oral medicines or insulin, inflammation can only be decreased by lowering LDL-C levels in micro vascular circulation diseases.

Alternative effective LDL-C lowering agents in statin hyper sensitivity or intolerant patients from side effects, may be explored.

The goal is as low LDL-C levels as possible, as continuous LDL- C influx in the vessel walls due to leaky / inflamed endothelium regardless of serum levels engages in ongoing inflammation.

Proprotein convertase subtilisin / Kexin type 9 (PCSK 9) inhibitor may be promising as a single agent in statin intolerant / hypersensitive patients or as an adjunct if high intensity doses of statins do not achieve significant LDL-C reduction.

4. Role of antioxidants.

So far clinical trials of antioxidants supplements including Vitamins C and E have not confirmed the benefits. As discussed in the section of oxidative stress, it is likely that in these patients the burden of oxidative stress is enormous due to ox LDL generation that antioxidant mechanisms are overwhelmed and are not adequate. Once the LDL -C levels are lowered and oxidative stress is reduced, addition of antioxidants may contribute to decrease inflammation. They may be useful in ageing which is associated with low grade inflammation and oxidative stress, in addition to lifestyle interventions and low dose statins.

5. Symptomatic treatment in all of these conditions with macro vascular and micro vascular circulation is continued such as antiplatelet agents, anti-hypertensive medicines and replacement therapy.

In case of macro vascular disease interventions such as PCI / CABG may be indicated for focal stenosis in acute coronary syndromes.

6. The patients with systemic inflammation as a result of chronic stress may not be symptomatic in spite of ongoing inflammatory activity, acute stress may amplify the stress response to severe rapid inflammation and by the time adaptive immunity responds which takes several days significant damage might have been ensued.

Use of high dose statin before anticipated stress has been found to decrease the development of adverse events in a study.

Inhibition of inflammation mediated the protective effects of Atorvastatin reload in patients with coronary artery disease undergoing non cardiac surgery. The results showed.

- Acute heart failure during hospitalization occurred in 5.2% of patients in the atorvastatin reload group and 11.2% in the placebo group. (P=0.0225).

- MACE during hospitalization occurred in 2.4% of patients in the Atorvastatin group and 8.0% in the placebo group (P=0.0088).

- According to multivariate analysis Atorvastatin reload conferred a 50% reduction in the risk of acute heart failure during hospitalization (Odds ratio, 0.50, 95% confidence interval 0.2-0.8; P= 0.005).

- The median decrease in the high sensitivity C-reactive protein and Interleukin -6 levels was significantly greater in the Atorvastatin reload group (P=0.001) [50-52].

The role of other anti-inflammatory agents may be explored in acute episodes of inflammation to prevent the tissue damage, steroids have been used in bronchial asthma and osteoarthritis exacerbations.

hs-CRP levels may help to determine the acute episode, while the inflammation is already in progress, ox LDL load increases with severity of insult, aggressive LDL reduction helps lower the inflammatory process, however other anti-inflammatory agents may be considered.

Conclusion

The cardiovascular diseases develop as a result of chronic psychosocial stress, triggering stress response which activates HPA and SAM axes, the innate immune response sets in, resulting in systemic inflammatory state. This results in lipid mediated auto immune state by producing ox LDL auto- antigens. These mount further innate immune responses and pattern recognition is presented for adaptive immune response. Series of events involving generation of inflammatory markers develop inflammation in vascular walls. The process is global, affecting both macro vascular circulation as atherosclerosis and micro vascular circulation as tissue damage with disease onset having serious health implications.

The process is long, smoldering and varies in its manifestations from low to moderate to severe intensity due to chronic stress and life style factors.

This may very well be considered as auto immune disease as pathophysiology involves auto antigens. The conventional auto immune diseases ie rheumatoid arthritis and systemic lupus may fall under the same umbrella as these diseases may be representing the spectrum of chronic higher degree of stress with more fulminant immune response.

The innate immunity for pathogens is diminished and there is increased incidence of cancer.

The cardiovascular disease burden results in considerable morbidity and mortality. The addition of all the micro vascular diseases is going to increase it substantially.

Aggressive efforts should be launched in prevention and risk factor modification. Life style changes, with non atherogenic diet, increased physical activity and tobacco cessation must be addressed through public health care disciplines.

Lipid management with pharmaceutical agents is the cornerstone of the primary and secondary prevention.

Primary prevention should be set as a priority to prevent devastating consequences of these diseases, which affects the whole body.

Last but not the least effective stress management strategies need to be incorporated in every individual's life as community and health care providers.

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