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Newer Risk Factors for Pre-Mature Coronary Artery Disease in Young Indians

Dr. Rajeev Gupta
Deptt of Cardiology, Gandhi Medical College
Cardiac Science Centre GMC - Bhopal, MP, India - 462001

Abstract : Although a number of conventional risk factors have been identified over the past several decades, the precise aetiology and mechanisms leading to the development of Coronary Artery Disease (CAD) remain incompletely understood. Increasing recognition that many patients with established CAD lack these conventional risk factors has led to a search for additional newer risk factors that may predispose individuals to CAD. Observational and epidemiological studies have identified a host of new and potential risk factors for athero-thrombotic vascular disease including increased Carotid Intima Media Thickness, elevated blood levels of homocysteine, fibrinogen, inflammation and infection, atherogenic lipoprotein phenotype associated with small low-density lipoprotein. (LDL) cholesterol particles and elevated triglycerides, elevated levels of lipoprotein (a) (Lpa), insulin resistance syndrome (syndrome X or Reaven's syndrome) and psychosocial factors. Predisposing genetic polymorphisms are of particular interest.

Keywords: Coronary Artery Disease (CAD), Lipoprotein (a) (Lpa), low-density lipoprotein. (LDL), Acute Coronary Syndrome (ACS)

During the last millennium both bio technological and technological advancements made a great revolution in the diagnosis and treatment of many heart diseases.(Gupta 2011)

Coronary artery disease (CAD). resulting from atherosclerosis and thrombosis (atherothrombosis) is the leading cause of death and morbidity in the industrialized world and is rapidly achieving the same dubious distinction in developing nations as well. In the cardiovascular field risk assessment and prevention of CAD remains the paramount objective of clinical practice as well as targets of ongoing research. The precise aetiology and mechanism(s) leading to the development of Cardiovascular diseases remain incompletely understood although a number of risk factors have been identified over the past several decades. These include abnormal levels of circulating cholesterol with elevated levels of Low Density Lipoprotein (LDL) and reduced levels of High Density Lipoprotein (HDL), hypertension, cigarette smoking, diabetes, male gender, postmenopausal state, advancing age, sedentary lifestyle, obesity and a positive family history of premature vascular disease. Increasing recognition that many patients with established CAD lack these conventional risk factors has led to a search for additional new risk factors that may predispose individuals to CAD. In a study of 101 patients undergoing coronary angiography at AIIMS, New Delhi, Lp(a) levels were higher in patients with CAD (27 mg/ dl vs. 15 mg/dl), Compared to patients without CAD) and better predictor of the presence of CAD than all other factors. In addition Lp(a) levels had a graded association with CAD, with 66% of patients in the lowest quartile having CAD compared with 100% in the highest quartile(Gupta R 1996) . Over the past several years, observational and epidemiological studies have identified a host of new and potential risk factors for athero-thrombotic vascular disease. Of this growing list of new and emerging risk factors. Increased carotid intima media thickness elevated, blood levels of homocysteine, fibrinogen, inflammation and infection, atherogenic lipoprotein phenotype associated with small low-density lipoprotein. (LDL) cholesterol particles and elevated triglycerides, elevated levels of lipoprotein (a) (Lpa), insulin resistance syndrome (syndrome X or Reaven's syndrome), psychosocial factors and a number of genetic polymorphisms are of particular interest. (Table - I)

Cartoid Intima Media Thickness (CIMT):

Thickening of carotid intima media thickness at any local site is generally considered to be an early marker of generalized atherosclerosis. The quantitative assessment of atherosclerosis in populations is essential for a better understanding of the patho-physiology of this disease and for the consequent development of optimal disease prevention strategies. The extent in severity scores for CAD were all positively correlated with CIMT($p<0.0001$) (Gupta, 2013 a, b and Gupta & Gupta 2013).

In patient undergoing coronary angiography, carotid intima media thickness is associated with increasing severity of coronary artery disease. This association is independent of other conventional cardiovascular risk factors. (Gupta, 2013)

Carotid intima media thickness is measured on ultrasonographic assessment of the carotid arteries. The upper limit of normal value for carotid intima media in

healthy adults is upto 0.8mm. It is being studied as a possible cardiovascular risk factor.

Hyperhomocysteinaemia

Elevated circulating levels of a sulfur-containing amino acid, homocysteine, a product of methionine metabolism, are associated with increased risk of CAD, ischaemic stroke, and peripheral vascular disease(Robinson *et al.,* 1998). Mild hyperhomocysteinaemia also appears to increase the risk of venous thrombosis, especially in presence of Leiden type mutation of the coagulation Factor V gene.

The first clue to homocysteine's role in cardiovascular disease came from the observations of McCully in 1969 when they described autopsy findings in two children with the syndrome of Homocysteinuria resulting from a rare genetically determined enzyme deficiency (McCully, 1969) . These children had marked elevations of plasma and urinary homocysteine due to deficiency of an essential enzyme (cystathionine beta synthetase) and extensive atherosclerosis and thrombosis. Folic acid, vitamin B_6 and vitamin B_{12} are essential co-factors involved in the metabolism of homocysteine. Mild to moderate elevations of plasma homocysteine levels are often due to either nutritional deficiency involving folate, vitamin B_{12} and vitamin B_6 or genetic abnormalities involving polymorphisms of key enzymes involved in homocysteine metabolism (such as methylene tetrahydrofolate reductase or MTHFR) or a combination of the two. In addition, renal failure, niacin and other drugs used in organ transplant patients may also raise plasma homocysteine levels. In some subjects, with normal fasting homocysteine levels, excessive increases following a standard challenge with methionine may uncover abnormal homocysteine metabolism. The magnitude of CAD risk associated with hyperhomocysteinaemia appears to be comparable to that associated with cigarette smoking and untreated hyperlipidaemia. Furthermore, high homocysteine levels seem to augment the deleterious effects of smoking and hypertension particularly in women. Elevated plasma homocysteine levels are also associated with increased mortality in patients with established CAD. In the Stroke Prevention in Young Women study, women whose homocysteine levels were in the top 10th percentile (greater than 11 nmol/ml) had nearly triple the risk of stroke, a risk comparable to that associated with smoking a pack of cigarettes daily.

Homocysteine may contribute to vascular damage by its deleterious effects on endothelial function, its prothrombotic, pro-oxidant and mitogenic effects. Based on the epidemiological relationship between hyperhomocysteinaemia and CAD, many physicians empirically use vitamin B supplementation (Folic Acid with or without Vit B_{12} and Vit B_6) to lower elevated plasma homocysteine levels. During a 14-year follow up in the Nurses Health Study, the risk of coronary heart disease was reduced in a graded fashion as intake of folate and vitamin B6 increased (Rimm *et al*., 1998). These results were maintained even after controlling for factors such as vitamin E intake and cigarette smoking. However, it should be pointed out that the relationship between homocysteine levels and CAD does not necessarily imply a cause and effect, and Vitamin B complex supplementation may produce benefits by mechanisms other than homocysteine lowering.

Lipoprotein(a) (Lp(a)) :

High levels of Lp(a) are evolving to be another genetically linked risk factor in thrombosis. Lp(a) consists of one molecule of apolipoprotein (b) linked by disulfide bonds to apolipoprotein(a), [apo(a)], which displays a significant homology to plasminogen. Apo(a) competitively binds to plasminogen receptors and inhibits the conversion of plasminogen to plasmin. The inhibition of the naturally occurring t-PA creates a prothrombotic state, resulting in local thrombus formation. The reduced generation of circulating plasmin also decreases degradation of thrombin. Lp(a) also enhances the synthesis of PAI-1 in the endothelium. High levels of Lp(a) have been identified within the atherosclerotic plaque, and may represent an important link between atherogenesis and thrombogenesis. Lp(a) as such plays a crucial role in the evolution of atheroma and the expression of acute clinical events. Elevated Lp(a) level is also a powerful risk factor for thromboembolism in childhood (Nowalk-Gottel *et al*., 1997), Lp (a) levels >20 to 30 mg/dL are associated with 2 to 3-fold increase in the risk of CAD. In a study of 90 consecutive cases of CAD it was observed that the Lp(a) levels are high in CAD cases. (Gupta, 2002)

In a study of CAD risk factors in Asian Indians living in the UK and their sibling in India serum Lp(a) levels were similar in the UK and India but significantly higher than Whites(Bhatnagar *et al*., 1995).In a study of 101 patients undergoing coronary angiography at AIIMS, New Delhi, Lp(a) levels were higher in patients with CAD (27 mg/ dL vs. 15 mg/dL in patients without CAD) and better predictor of the presence of CAD than all other factors. In addition Lp(a) levels had a graded association with CAD, with 66% of patients in the lowest quartile having CAD compared with 100% in the highest quartile (Gupta *et al*.,1996). Importantly, elevated Lp (a) levels can be lowered with oestrogen replacement therapy in women and by niacin. There is also a suggestion that intake of fish and fish oil can lower Lp (a) as well as factor VII and blood viscosity.

Small Dense LDL: (Atherogenic Lipoprotein Phenotype or LDL – Phenotype B)

A study of 150 normal healthy persons as controlled compared with 150 cases of established cases of CAD suggested that there is a significantly high prevalence of dyslipidaemia in a healthy central Indian population and it is relatively higher in cases of CAD (Gupta *et al*., 2002). Circulating LDL- cholesterol particles are heterogenous and based on gradient gel electrophoresis, they have been characterized into small and densely packed particles

(small dense LDL and large buoyant particles (large or fluffy-puffy LDL). The LDL cholesterol profiles are categorized as phenotypic patterns A, B, or C. Patients with pattern A have primarily large LDL cholesterol particles. Patients with Pattern B have mostly small, dense LDL particles, and patients with pattern C have a mix of large and small LDL particles. Small, dense LDL particles have been causally linked to an increased risk of CAD independent of total and LDL-cholesterol levels(Stampfer *et al*.,1996).The phenotype B pattern is often but not always associated with elevated triglycerides and triglyceride-rich lipoproteins (chylomicron-remnants and intermediate density lipoproteins), reduced HDL cholesterol and other features of the insulin resistance syndrome; thus the relationship between small dense LDL and CAD risk may in part be related to these associated metabolic abnormalities. It has been suggested that small dense LDL particles are more atherogenic because of greater arterial wall retention and increased susceptibility to oxidation. Phenotype pattern B appears to be a largely genetically determined trait with a clear environmental influence that is more common in men than women.

While evidence linking LDL-phenotype B to an increased risk of CAD is mounting, the precise therapeutic implications of this-phenotype remain to be clearly defined. Recent evidence suggests that pattern B patients are more responsive to reductions in cholesterol levels with a reduced dietary fat intake compared to pattern A subjects(Krauss & Dreon, 1995).Statins, which are so effective in lowering levels of larger LDL particles, do not consistently reduce small dense LDL. Fibric acid derivatives and nicotinic acid tend to reduce the levels of small, dense LDL cholesterol particle concentrations but it is unclear whether such a change plays a role in the beneficial effects independent of changes in triglycerides and HDL. Additional studies are needed to clearly define the therapeutic implications of LDL pattern B phenotype.

Triglycerides

Hypertriglyceridaemia has also been considered to confer increased risk for CAD (Austin *et al*., 1988). Since hypertriglyceridaemia is often observed in association with small dense LDL phenotype, low HDL and other phenotypic features that characterize the insulin-resistance syndrome, it is difficult to ascribe the increased risk associated with hypertriglyceridaemia to any single metabolic abnormality (Gupta, 2004). Some studies, however, have suggested that hypertriglyceridaemia is an independent risk factor for CHD, even after adjustment for high-density lipoprotein (HDL cholesterol levels (Austin *et al*., 1988). Elevated triglyceride levels can be reduced by weight loss, reduction in alcohol consumption, use of niacin, fibrates, fish-oil and large doses of statins. However, clinical trials have not yet assessed the actual cardiovascular benefits of lowering triglyceride levels independent of changes in other associated metabolic abnormalities. Nevertheless, since triglyceride levels over 1000 mg/dl are associated with an increased risk of pancreatitis, prompt drug treatment is generally recommended.

The Deadly Lipid Quarlet and Lipid Tetrad Index

Lp(a) is a powerful independent risk factor of coronary artery disease. Its effects get multiplied by high TG, high LDL-C and low HDL-C. This constitutes a "deadly lipid quartet' and may help explain high premature coronary artery disease in Asian Indians(Nowalk-Gottel *et al*.,1997) it also explains the African paradox of Lp(a), who inspite of having high Lp(a) have lower rates of CAD.The adverse effects of Lp(a) in them gets mitigated by low LDL, low TG and high HDL levels.

Enas and Mehta (1995) has proposed a comprehensive lipid Tetrad Index to ascertain the total burden of dyslipidaemia in Indian. This explains the different incidence of CAD amongst the different ethnic groups and resolves the Japanese paradox (high smoking rates yet low CAD mortality), Chinese paradox (high Smoking and hypertension rates yet low CAD mortality), African-American Paradox (higher incidence of obesity, malignant hypertension and diabetes yet low incidence of CAD) and American Indian paradox (Pima Indians) have, highest incidence of diabetes yet lowest CAD rates. Comprehensive lipid tetrad index is calculated by the formula TC x TGx Lp (a)- HDL-C. The values are taken as mg / dl. An index <10,000 is desirable, 10,000-20,000 boderline abnormal and > 20,000 as high

Tissue- Type Plasminogen Activator (t-PA):

t-PA is synthesized in the endothelial cells, and is an important anticoagulant. In the presence of endothelial dysfunction, fibrinolyis is retarded in the arteries rendering them ripe for fibrin deposition and development of a thrombus. Following thrombolysis, there is extensive damage to the endothelial lining, this may also explain the occurrence of re-occlusion following successful thrombolytic therapy. Plasma levels of rt-PA appear to be inversely related to high-density lipoprotein cholesterol (HDL-C) levels.

Plasminogen Activator Inhibitor-1 (PAI-1):

Plasminogen activator inhibitor-1 (PAI-1) is a single chain glycoprotein that forms stable complexes with rt-PA and urokinase-type plasminogen activator, and inhibit fibrinolytic activity. Its levels are highly correlated with serum triglycerides levels (Mehta et al., 1997). Because of its procoagulant effect, high levels of PAI-1 serve as a marker of increased thrombogenesis. Recent studies indicate an inverse relationship between PAI-1 and dietary fibre, and the cardioprotective effect of high fibre diet may be mediated through lowering the PAI-1 levels (Djoussse L, 1998). High levels of PAI- 1 are highly predictive of premature CAD in Whites and may contribute to the high rates of CAD among Asian Indians (Enas & Mehta, 1995). However, additional studies need to be conducted to determine PAI-1 levels in different populations.

Fibrinogen, Factor VII and Blood Viscosity:

Serum fibrinogen level, coagulation factor VII activity, and blood viscosity are some of the well studied haemostatic risk factors for CAD (Ridker & Henneken, 1991). Fibrinogen is a cofactor for platelet aggregation. Fibrinogen levels are higher in patients who develop ACS or CAD deaths. This association is independent of other coronary risk factors and has the same predictive value as elevated serum cholesterol levels, Fibrinogen levels are also correlated with the risk of stroke as *well* as the degree of atherosclerosis in coronary, carotid, femoral arteries and aorta. Fibrinogen levels increase during colder months and in smokers, whereas the levels decrease with alcohol intake, and exercise.

Elevated levels of factor VII as well as obesity and physical inactivity are inversely correlated with fibrinolytic activity, high plasma levels of the factor VII were associated with an increase in the risk of ACS in several studies. The CAD risk with high levels of Factor VII is further accentuated by the presence of additional risk factors, especially diabetes, high cholesterol, and triglycerides. A major determinant of factor VII level is dietary fat intake. Recent studies indicate that elevated plasma viscosity levels may be an independent risk factor for CAD (McLaugin *et al*., 1996), Plasma viscosity is highly dependent upon haematocrit, fibrinogen, alpha 2 macroglobulins, immunoglobulin M and triglycerides levels. The pathogenicity of elevated triglycerides appears to be partly mediated by increased viscosity.

Platelet Activity: Platelets play a crucial role in endothelial function, coagulation, and thrombosis. The participation of platelets in the thrombotic process depends on their ability to adhere to an abnormal surface and aggregate to form an initial platelet plug. The activation of the platelets stimulate further platelet aggregation and triggers the coagulation cascade. Both increased blood platelet number and increased platelet reactivity are associated with increased risk of CAD. Platelet agreeability is highest in the early morning hours and is enhanced by high fat diet and is reduced by aspirin therapy.

Antiphospholipid Antibody Syndrome (APLS):

Several studies link autoantibodies to increased procoagulant activity. Antiphospholipid antibody syndrome (APLS) may account for a third of new strokes occurring under the age of 50. Although the overall prevalence of APLS in patients who develop MI is about 5%, the syndrome is 2 to 3 times more common among young men and women with CAD and in those with coronary artery bypass occlusion.

Endothelial dysfunction:

Vascular endothelium is an active site of protein synthesis and may be considered the largest and most important paracrine organ in the human body. The endothelial cells synthesize, secrete, modify, and regulate connective tissue components, vasodilators, vasoconstrictors, anticoagulants, fibrinolytic compounds, and prostanoids, each contributing to the maintenance of the vascular tone, thromboresistance and physiological haemostasis.

Tissue Factor:

Synthesis of tissue factor (previously known as tissue thromboplastin) by the endothelial cells is markedly increased after mechanical or biochemical stimulation of the vessel wall. Tissue factor acts as an essential cofactor in the activation of factors IX and X, thereby triggering the coagulation cascade. Spontaneous and angioplasty-induced fractures of atherosclerotic plaques may trigger thrombosis by exposing circulating blood to procoagulant plaque elements previously sequestered within the vessel wall, especially the highly thrombogenic tissue factor. Intravascular trombosis plays an important role in the pathogenesis of ACS and in abrupt occlusion or restenosis of the coronary arteries following angioplasty and atherectomy. Coronary atherectomy is likely to create a surface that exposes active tissue factor to circulating blood.

Insulin Resistance Syndrome

Insulin resistance refers to a generalized metabolic disorder in which various tissues are resistant to normal level of plasma insulin. Metabolic abnormalities include defective glucose uptake by skeletal muscle, increased release of FFA by adipose tissue, overproduction of glucose by the liver and hyper secretion of insulin by pancreas. Hyperinsulinemia is associated with platelet dysfunction, decreased fibrinolytic activity, increased smooth muscle cell proliferation. Insulin potentiates the action of platelet derived growth factor (PDGF) which causes smooth muscle proliferation. The insulin resistance syndrome is characterized by abdominal obesity (apple body configuration), impaired glucose tolerance, hyperinsulinemia, high TG, low HDL-C and hypertension. The excess burden of CAD in Indians can be explained by insulin resistance syndrome. The higher serum uric acid positively correlates with no. of components of metabolic syndrome with hypertension and obesity being the major determinants of hyperuricaemia. (Gupta *et al*., 2011)

Inflammation and Infectious Agents

There is substance evidence that inflammation plays a key role at various stages of atherothrombosis including the process of plaque disruption and thrombosis. Inflammatory cells in the plaque may contribute to plaque destabilization by processing matrix degrading metalloproteinases and by inducing smooth muscle cell apoptosis. Inflammatory cells also contribute to plaque-thrombogenicity by releasing tissue factor, a procoagulant protein that activates the clotting cascade resulting in thrombin generation which leads to platelet aggregation and fibrin deposition. Mitogenic cytokines released by inflammatory cells may also influence the growth of atherosclerotic plaque. Elevated C- reactive protein has also been shown to confer an increased risk of recurrent

coronary events in patients with established CAD and unstable angina (Danesh *et al*., 1998). Although C-reactive protein is a systemic marker of inflammation, its pro-inflammatory and pro-thrombotic effects have led to the suggestion that it may bear a causal link to CAD risk. Other inflammatory markers such as serum amyloid A, Interleukin-6 and Leukocyte adhesion molecules such as ICAM-1 (intercellular adhesion molecule land VCAM (vascular cell adhesion molecule) have also been shown to demonstrate similar trends.

Inflammation in atherosclerotic plaque may be incited by a number of factors, which include oxidized LDL, cigarette smoking and possibly infectious agents. Oxidized LDL has been identified in experimental as well as human atherosclerotic plaques. In cell culture studies as well as *in vivo* models, oxidized LDL activates a number of pro-inflammatory genes in the vascular wall cells, which in turn can recruit mononuclear cells into the vessel wall as well as activate them (Berliner *et al*., 1995). Some of the clinical benefits of lipid lowering may result from a reduction in inflammation due to a decrease in LDL and LDL oxidation.

Infectious agents such as Herpes virus, CMV, *Chlamydia pneumonia* and *H.pylori* as well as remote infections such as chronic bronchitis and chronic gingivitis (most often due to infection with *Porphyromonus gingivalis*) have all been linked to atherosclerotic vascular disease and acute coronary events based on sero-epidemiologic data and /or identification of the organism in the atherosclerotic plaque, Infectious agents may contribute to vascular disease by inducing inflammation within the atherosclerotic plaque thereby contributing to plaque disruption, thrombosis and acute ischaemic syndromes. Of all the infectious agents, *C.pneumonia* has provoked the greatest interest as a potential culprit in athero-thrombosis. Recent studies have identified the presence of *C.pneumonia* inside macrophages in human atherosclerotic plaques in 40-50% of cases (Ridker, 1998).

Psychosocial Factors

A number of recent studies provide persuasive evidence regarding the role of anxiety, depression, hostility, rage and social isolation as prognostic factors in heart disease. Some people appear to tolerate psychosocial stress better than others. Hot reactors show a greater increases in blood pressure and pulse rate when challenged by stressful tasks such as public speaking or timed mathematical computations and it has been -suggested that emotional stressors act as triggers of catastrophic cardiovascular events. These reactions have been linked to elevated cardio vascular disease risk. Adverse life events producing anxiety and depression are often reported by patients to have occurred preceding a myocardial infraction (MI) (Gupta *et al*., 2011). Correlation of anxiety and depression with loss of autonomic control heart rate, impaired baro reflex sensitivity and emotional trigger influencing the presentation pattern of ischaemia and arrhythmias in CAD (Gupta, 2013 a, b)

Genetic polymorphisms

It is generally agreed that genetic factors play an important role in influencing the risk of Cardio vascular disease. Many of these genetic factors result from variations in genes that regulate lipoprotein and cholesterol levels but in recent years, a number of genetic variations (polymorphisms) affecting a number of non-lipoprotein related genes, resulting in phenotypic alterations, and altered risks for CAD and CAD events in specific populations have been identified. Many of these polymorphisms involve genes, associated with haemostatic/fibrinolytic functions. Thus polymorphisms in the genes encoding platelet glycoprotein receptors, plasminogen, plasminogen activator inhibitor -1 (PAI-1), factor VII and factor VIII, fibrinogen, angiotensin converting enzyme (ACE) and angiotensinogen, methylene tetra hydrate folate reductase (MTHFR) related to homocysteine metabolism, endothelial nitric oxide etc. have been linked to an enhanced risk of atherothrombotic events (Becker *et al*., 1998).

In addition, two genetic polymorphism involving paraoxonase, an antioxidant HDL-associated enzyme and stromelysin-1, a matrix degrading metalloproteinase produced by inflammatory cells and implicated in plaque disruption, have also been identified and linked to risk of CAD and CAD events. With the race to identify all of the nearly 70,000 human genes, that is currently going on. We can look forward to gaining a clearer understanding of the role of specific genes in cardiovascular disease. This is likely to lead to new preventive and therapeutic strategies that have the potential to revolutionize the practice of medicine.

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Table – I : Newer Risk Factor for Premature CAD in Young Indians	
Carotid Intima Media thickness (CIMT)	Platelet activity
Hyperhomocysteiniamia	Antiphospholipid antibody syndrome
LDL phenotype B	Endothelial dysfunction
Hypertriglyceridemia	Tissue factor
Tissue type Plasminogen activator (t-PA)	The Deadly Lipid Quarlet and Lipid Tetrad Index
Plasminogen activator Inhibitor - 1 (PAI - 1)	Insulin resistance Syndrome
Elevated lipoprotein(a) : Lpa	Inflammation and infectious agents
Hyperfibrinogenemia, Factor VIII and Blood viscosity	Psychosocial factors
	Genetic polymorphisms