Risk Factors for Coronary Artery Disease in Indians: Emerging Trends

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Introduction

The prevalence of coronary artery disease (CAD) is known to be very high both among migrant Asian Indians and also among people within the Indian subcontinent. Moreover, CAD in Asian Indians occurs prematurely, i.e., at least a decade or two earlier than that seen in Europeans. A host of new risk factors related to the metabolic syndrome have been described in Asian Indians, including an excess of non-insulin dependent diabetes mellitus (NIDDM), increased upper body obesity with an increased waist-hip ratio (WHR), elevated plasma insulin levels (hyperinsulinaemia) and increased insulin resistance.

The precise etiology and mechanisms leading to development of CAD, however, remain incompletely understood although an increasing number of risk factors have been identified over the past several decades. These include abnormal levels of serum cholesterol with elevated levels of LDL and reduced levels of HDL cholesterol, serum triglycerides, hypertension, cigarette smoking, diabetes, male gender, post-menopausal state, advancing age, sedentary lifestyle and family history of heart disease. Increasing recognition that many patients with established CAD lack these traditional risk factors has led to a search for additional new risk factors that may predispose individuals to CAD. This article reviews the current status of conventional and the emerging risk factors for CAD.

Conventional Risk Factors

Smoking, elevated lipid levels, increased blood pressure, higher glucose, lack of physical activity, obesity and the psychosocial factors form a group of lifestyle risk factors associated with increased morbidity and mortality from CAD.

Smoking

Cigarette smoking is an important risk factor for CAD as it lowers HDL cholesterol, raises fibrinogen, aggregates platelets, decreases the oxygen-carrying capacity of the blood and causes release of catecholamines making the myocardium more irritable. Because of these effects, smoking precipitates coronary attacks and sudden deaths, particularly in those with other risk factors.

Lipids

Cholesterol. Epidemiological studies in western population have revealed that there is a consistent, strong, positive, continuous and graded relationship between plasma total cholesterol and the incidence of CAD. This holds true in all the ranges of total cholesterol starting from normal and mildly elevated levels. Both the primary and secondary intervention trials have shown reduction in all-cause mortality and morbidity by using lipid lowering technique particularly the statin group of drugs.

HDL Cholesterol. The concept of low HDL cholesterol as a major risk factor emerged from the Framingham heart study. The level of HDL cholesterol is inversely related to CAD incidence, consistent with its putative role in cholesterol removal. HDL levels are low in Indians with CAD. In the CAD study in USA, only 14 percent Asian Indian men and 5 percent women had optimal HDL cholesterol levels. Total cholesterol-HDL cholesterol ratio (> 4.5) is considered a powerful predictor of CAD.

Serum Triglycerides. The role of serum triglycerides continues to be debated as a CAD risk factor. Both fasting and non-fasting triglycerides levels were associated with risk in the Framingham and other investigations. The debate centres around whether total triglycerides are significantly associated with CAD risk after adjustment for HDL cholesterol in prediction equations. Hypertriglyceridaemia patients often manifest hypertension, hyperinsulinaemia, visceral obesity and impaired glucose tolerance (IGT) along with procoagulant state and atherogenic lipoprotein phenotype (small dense LDL...
particles), together constituting the insulin resistance syndrome, a very high risk state for CAD\textsuperscript{16,17}.

**Blood Pressure.** Hypertension is a well acknowledged risk factor for CAD and the systolic pressure is at least as important as the diastolic pressure. Isolated systolic hypertension is also now established as a major hazard for CAD and stroke\textsuperscript{18}.

**Diabetes and IGT**

Macrovascular disease is the main cause of mortality in people with type 2 diabetes\textsuperscript{19}. Many factors contribute to the high prevalence of macrovascular disease in diabetes. These include a host of proatherogenic abnormalities including diabetic dyslipidemia, elevated fibrinogen and plasminogen activator inhibitor-1 (PAI-1) levels as well as increased platelet aggregation. Diabetes is also associated with alteration in vascular endothelium, elevated levels of Von Willebrand factor and the plasma levels of endothelin-1 that predispose the vessels to atherogenesis.

The association of CAD with hyperglycaemia in fact starts even in the euglycemic range. Recent studies show that cut off points conferring risk of CAD are much lower than the levels at which diabetes is diagnosed today\textsuperscript{20}. The risk appears to start even below the levels of IGT\textsuperscript{21}.

**Insulin Resistance**

The clustering of insulin resistance and/or hyperinsulinemia, glucose intolerance, hypertension, hypertriglyceridemia and low HDL is referred to as "Insulin Resistance Syndrome" (Reaven's Syndrome or Syndrome X). The relation of insulin resistance to cardiovascular risk, particularly to CAD has been well established in many prospective studies\textsuperscript{22-24}. However, the association is complex and the pathways by which elevated insulin adversely affects both the CAD risk factors and the risk of developing CAD have yet to be elucidated.

A recent meta-analysis of prospective population-based case-control study examined the relation between insulin and cardiovascular disease\textsuperscript{25}. The meta-analysis revealed that insulin was a weak but positive indicator of cardiovascular risk. The relation is stronger in middle aged persons than in older ones. Using multivariate analysis, Pyorala et al\textsuperscript{26}, reporting 9.5 years' results for the Helsinki Policemen's Study, also found that high plasma insulin increased CAD risk independent of other risk factors.

The Quebec Cardiovascular Study provides the strongest evidence that hyperinsulinemia is associated prospectively with the development of CAD\textsuperscript{27}. This study clearly demonstrated that adjustment for other risk factors did not diminish the predictive power of insulin and that increased levels of both fasting insulin and apolipoprotein B (apo B) strongly predicted CAD.

Certain studies, however, provide contrasting views with regard to risk of CAD and hyperinsulinemia. Based on the Rancho Bernado Study in more than 1200 persons, Ferrara et al\textsuperscript{28} found that hyperinsulinemia did not increase the risk of fatal cardiovascular disease. In a study of nearly 600 men in their late 60s, Welin et al\textsuperscript{29} reported that fasting serum insulin was not an independent coronary risk factor. In view of the contrasting views regarding hyperinsulinemia and the risk of CAD, more studies, especially in the Indian population, are required to convincingly demonstrate that hyperinsulinemia is an independent risk factor for CAD.

**Newer Risk Factors**

**Lipoprotein (a) [Lp(a)]**

Lp(a) is a modified form of LDL that contains apo B 100 linked by a disulphide bridge to a highly polymorphic glycoprotein, apolipoprotein\textsuperscript{30}. Elevated levels of Lp(a) have been linked to an increased risk of CAD and other forms of vascular disease especially when associated with the elevated LDL or reduced HDL cholesterol level\textsuperscript{31}. A recent study by our group has suggested that serum Lp (a) is an independent risk factor for CAD in type 2 diabetic patients in South India\textsuperscript{32}.

**Haematologic Factors**

i. **Hyperhomocysteinaemia.** Elevated circulating levels of a sulphur containing amino acid, homocysteine, a product of methionine metabolism, are associated with increased risk of CAD, ischaemic stroke and peripheral vascular disease\textsuperscript{33}. High levels of homocysteine are injurious to endothelium, promote LDL oxidation and thrombus formation. A meta-analysis based on 27 studies involving 4,000 patients has shown that homocysteine is an independent graded risk factor for atherosclerotic vascular disease\textsuperscript{34}. However, recent studies in Indians suggest that homocysteine may not be a major risk factor in Indians in India\textsuperscript{35-38} and in Singapore\textsuperscript{39}, while for Asian Indians in UK it seems to be an important risk factor\textsuperscript{39}.

ii. **Fibrinogen.** Several observational studies have suggested that circulating fibrinogen is an independent risk factor for CAD and stroke. A meta-analysis based on 12 population-based studies and 6 studies involving patients with pre-existing vascular disease, suggests a consistent strong relationship between circulating
fibrinogen levels and CAD risk. The potential detrimental effects of fibrinogen may be related to its effect on plasma viscosity as well as the key role that fibrinogen plays in thrombosis. In Indians also, fibrinogen seems to be an important factor.

iii. TP A and PAI-1. Tissue type plasminogen activator (tPA) is an important anticoagulant synthesized in the endothelial cells. Plasma levels of tPA appear to be inversely related to HDL levels. Plasminogen activator inhibitor-1 is a single chain glycoprotein that forms stable complexes with tPA and inhibits fibrinolytic activity. Because of its procoagulant effect, high levels of PAI-1 serve as a marker of increased thrombogenesis. 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.

iv. Platelet Activity. Platelets play a crucial role in endothelial function, coagulation and thrombosis. Both, the increased platelet number and increased platelet reactivity are associated with increased risk of CAD. In one study, the relative risk of CAD with high platelet counts was higher than that of all other risk factors during a follow-up of 13.5 years. Markovitz et al. have also shown that platelet activation factor (PAI-1) may be one of the important factors contributing to CAD among Indians.

Inflammatory Markers and Infectious Agents

There is substantial evidence that inflammation plays a key role at various stages of atherosclerosis including the process of plaque disruption and thrombosis. Inflammatory markers such as C-reactive protein and leukocyte adhesion molecules have been shown to confer an increased risk of recurrent coronary events in patients with CAD.

Role of Chronic Sub-Clinical Infections

There is some evidence that microorganisms such as Chlamydia, H. pylori and Yersinia have a role in CAD. There is laboratory evidence, seroepidemiological studies, pathological studies and clinical trials to suggest their association. Clinical trials like ACES trial are in progress to reveal the efficacy of antibiotic treatment in prevention of CAD.

Microalbuminuria and CAD

Even though microalbuminuria is clearly associated with microvascular disease (nephropathy) in diabetes, recent studies have shown that diabetic patients with microalbuminuria have higher prevalence of CAD.

Microalbuminuria has thus recently been added to the growing list of components of the insulin resistance syndrome. However, more studies are required to show a clear cut association between microalbuminuria and CAD.

Implications of Risk Factors for Managing CAD

The control of risk factors for CAD involves a multifactorial approach that includes diet control, exercise, weight reduction, cessation of cigarette smoking and management of the components of metabolic syndrome.

1. Lifestyle Changes

a. Weight Reduction. Weight reduction by diet control and exercise play a big role in bringing down the risk factors for CAD in the dysmetabolic syndrome namely obesity, hyperlipidemia, dyslipidemia and diabetes. Weight reduction also brings about significant improvement in insulin sensitivity and thus reduces the risk associated with insulin resistance. Exercise not only reduces weight but also increases HDL cholesterol.

b. Cessation of Smoking. Cessation of smoking not only reduces the risk of CAD by a significant degree but also improves the metabolic profile, mainly dyslipidemia. Risk of coronary events has been found to be halved after cessation of smoking.

c. Epidemiologic data indicate a protective effect of alcohol intake. However, this benefit applies only at moderate intakes and is not seen with alcohol abuse.

2. Hypertension

Antihypertensives must be chosen appropriately as many antihypertensives like β-blockers (particularly the non-cardioselective ones) have unwanted metabolic effects on lipids and carbohydrate tolerance which can attenuate the benefit of blood pressure lowering. The usefulness of polypharmacy to aggressively treat hypertension, especially those with diabetes, has recently been brought out by the United Kingdom Prospective Diabetes Study (UKPDS). Drugs like ACE inhibitors, which do not appear to worsen lipid levels or glucose tolerance and which reduce microalbuminuria, appear ideal to treat hypertension.

3. Dyslipidemia

This condition must be aggressively treated. Although as per NCEP guidelines, goals for total
cholesterol and LDL cholesterol are 200 mg/dL and 130 mg/dL respectively, in view of the high risk for CAD in our population, lower goals probably need to be achieved. When non-pharmacological treatment is not effective, one should not hesitate to use drugs. Statins are the drugs of choice for elevated cholesterol and LDL cholesterol while fibrates are the preferred group of drugs for elevated serum triglyceride levels.

4. Hyperglycemia

UKPDS has shown that a reduction in HbA1c by 1 percent brings down the risk for CAD by 16 percent. In the treatment of hyperglycemia, the role of metformin and thiazolidinediones appear promising as they not only decrease hyperglycemia but also improve insulin sensitivity.

5. Miscellaneous

Increased vitamin intake (especially folic acid) in the diet or through supplementation has been found to decrease homocysteine levels and improve CAD and other vascular disease risk. The role of antioxidants is still not clear. However, some studies suggest that high doses of vitamin C and vitamin E might be of some benefit. Aggressive treatment of infections with Helicobacter pylori and Chlamydia might reduce the risk of CAD due to these infections although more data is needed to substantiate it.

Conclusion

Atherosclerotic coronary artery disease is clearly multifactorial in its aetiology reflecting a complex interaction between a multitude of genetic and environmental factors. Over the past several years, in addition to classic and well established risk factors, a series of new risk factors have been identified. An understanding of the risk factors that lead to the development of CAD in Indians could help to develop strategies for reducing the CAD epidemic which is looming large as we enter the new millennium.

References