INTRODUCTION

Diabetes has threatened our country with its epidemic nature and problems, and India has the dubious distinction of being the “Diabetes Capital of the World”. Today, the medical community unhappily accepts, and the public should advisably be aware, that diabetes is a coronary heart disease risk equivalent. Diabetes leads to microvascular disease (retinopathy, nephropathy, and neuropathy), and macrovascular disease (atherosclerotic coronary, cerebral, and peripheral vascular disease). And this diabetic macroangiopathy is responsible for 80% of mortality and 75% of hospitalization in the diabetic population. Consequently, the clinicians and research workers have great interest in assessing whether preventive measures and treatment strategies have any effect on the regression of coronary atherosclerosis.

DIABETES AND CORONARYATHEROSCLEROSIS

Diabetes dramatically accelerates the atherosclerotic process by driving inflammatory process coupled with metabolic and vasculotoxic effects in a prothrombotic milieu. Diabetics have 3 to 5 times higher risk of coronary heart disease death than nondiabetics. A diabetic has a risk that is similar to that of a nondiabetic patient with myocardial infarction. Diabetes also nullifies the cardiovascular protective effect which women usually enjoy in the premenopausal period.

Following acute coronary syndrome, diabetics fare worse compared to nondiabetics, as diabetics have higher rates of stroke, heart failure, and also more complications following coronary intervention.

PATHOPHYSIOLOGY OF DIABETIC VASCULAR DISEASE

Diabetes with its metabolic abnormalities of hyperglycemia, dyslipidemia, and insulin resistance disrupts the function of endothelium, smooth muscle cells, and platelets which in turn promotes atherosclerotic process.

Inflammatory cytokines released from the adipose tissue result in insulin resistance and also impair endothelial dysfunction. The excess adipose tissue that usually accompanies diabetes releases excess of fatty acids which also impair endothelial dysfunction and produce insulin resistance.

Hyperglycemia, free fatty acids, and insulin resistance in a diabetic lead to increased oxidative stress, protein kinase C activation and RAGE (receptors for advanced glycation end products) activation, leading to vasoconstriction, inflammation, and thrombosis. There is thus heightened atherothrombotic tendency in diabetics.

Understanding the processes involved in the development of atherosclerosis in diabetics offers various therapeutic targets.

REGRESSION OF Atherosclerosis

Definition of regression of atherosclerosis: “Regression is not merely a rewinding of progression, but instead involves emigration of the maladaptive infiltrate, followed by the initiation of a stream of healthy, normally functioning phagocytes that mobilize necrotic debris and all other components of advanced plaques.”

For a clinician, probably a more generalized and practical definition would be different. Any change in the atherosclerotic lesion that is favourable and that improves the course of the disease can be called “regression”. Ideally the lesion should completely
Regression of Coronary Atherosclerosis in Diabetes: Fact or Fiction?

There is some skepticism whether atherosclerosis can regress. It is felt (by these pessimists?) that lesion components like necrosis, fibrosis and calcification are irreversible. But there is enough evidence that is accumulating from animal studies and from better imaging modalities used in patients that it is a fact and not a fiction.

**EVIDENCE FROM ANIMAL STUDIES**

In 1976, Armstrong, summarizing the studies on primates stated that,” In the primate the answer is clear: all grades of induced lesions studied to date improve….the primate lesion shows amazing metabolic responsiveness: some extracellular as well as intracellular lipid is depleted, there is resolution of necrotic lesions, crystalline lipid tends to diminish slowly and fibroplasia is eventually contained.” (5)

From the various animal studies, including the popular Apo E knock out mice studies, it was concluded that raising plasma functional HDL levels through enhanced apoA-1 is sufficient to favourably remodel atheromatous lesion, a larger benefit is achieved when high levels of functional HDL are combined with large reductions in the apoB lipoproteins.

**EVIDENCE FROM CLINICAL STUDIES**

Angiographic paradox: Most of the clinical studies involving imaging modalities to assess the regression of atherosclerosis have highlighted an interesting finding. Though the angiographic regression is small, the clinical benefit is substantial. This lead to the coining of the term “angiographic paradox”. The explanation is that while the therapeutic strategies produce a small but statistically significant shrinkage of angiographically prominent stable plaque lesions, they would also be stabilizing the smaller vulnerable plaques in the rest of the coronary tree.

Methods to document regression of atherosclerosis: the various imaging modalities that assess the regression are:

- Quantitative coronary angiography
- Coronary calcium score by CT scan
- MRI Imaging
- Intravascular Ultrasound
- Perfusion scan

**CLINICAL STUDIES**

The Lifestyle Heart Trial: (6) In this study, 28 patients were assigned to experimental group of low fat vegetarian diet, no smoking, stress management and exercise, and were compared to usual care control group. After 1 year, 195 coronary artery lesions were studied. Overall, 82% in the experimental group showed atherosclerotic regression, whereas the control group showed progression of atherosclerosis.

**HATS: (HDL Atherosclerosis Treatment Study): (7)** In this study, simvastatin plus niacin combination therapy lowered LDL-cholesterol by 42% and raised HDL cholesterol by 26%. A 0.4% decrease in angiographically detected stenosis resulted in 87% decrease in cardiovascular events. This substantial benefit probably reflects favourable change in the plaque biology.

**REVERSAL: (Reversal of Atherosclerosis with Aggressive Lipid Lowering study): (8)** High dose statin was compared with conventional dose in acute coronary syndrome patients. After 18 months of treatment, atheroma progressed significantly by 2.7% in conventional dose arm despite achieving LDL target. High dose statin reduced LDL cholesterol further and there was no significant progression of atheroma.

**ASTEROID: (A Study to Evaluate the Effect of Rosuvastatin on Intravascular ultrasound Derived Coronary Atheroma Burden): (9)** All acute coronary syndrome patients received high dose statin therapy for 24 months. Pre and post-treatment IVUS findings were compared. LDL cholesterol was reduced to 60 mg% and there was a shrinkage of atheroma volume by 6.8%. In this study, 13% of the subjects were diabetics.

Both REVERSAL and ASTEROID studies showed that aggressive lowering of LDL cholesterol produces shrinkage of established plaques. In ASTEROID study, higher HDL cholesterol levels were achieved, resulting in greater efficacy (Fig 2).

**ARBITER STUDY: (Arterial Biology for the Investigation for the Treatment Effects of Reducing Cholesterol): (10)** This study utilized carotid intima media thickness (CIMT) as a surrogate for coronary artery disease risk and compared statin-niacin combination with statin alone. Niacin raised HDL cholesterol by 23%. In the statin group, CIMT increased, while in the statin plus niacin group, CIMT decreased by 0.041 mm at 24 months. In this
study, 28% were diabetics.

PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary obstruction Prospective evaluation): (11) 543 patients with Type 2 diabetes were randomized to receive either glimeperide or pioglitazone for a period of 18 months. IVUS studies were done at baseline and at 18 months (Fig 2).

Mean percent atheroma volume decreased by 0.16% in the pioglitazone group, but increased by 0.73% in the glimeperide group. Patients in the pioglitazone group were more likely to develop edema, weight gain and bone fractures. This is probably the first time a diabetes study has shown to slow progression of coronary atherosclerosis.

CONCLUSION

Available data suggest that coronary atherosclerotic process in diabetes is reversible and is a reality and not a fiction. Therapeutic strategies have to be aggressive and comprehensive. (Fig 3)

REFERENCES