ABSTRACT

Coronary heart disease is the single largest cause of death in India and causes large premature mortality and morbidity. Risk factors include smoking, tobacco use, high blood pressure, diabetes, high LDL cholesterol, low HDL cholesterol and sedentary lifestyle. Diabetes is a major cardiovascular risk factor and is epidemic in India. Atherosclerotic vascular disease is the major cause of mortality and morbidity in patients with type 2 diabetes. More than 60% of type 2 diabetes die of coronary heart disease and type 2 diabetes is a major cardiovascular risk factor and in India more than 60% patients with coronary heart disease have diabetes or glucose intolerance. There are macrolevel as well as microlevel mechanisms linking the two diseases. At a macrolevel the sociological (rapid urbanization, rapid affluence), demographic (increased aging) and epidemiological factors (sedentary lifestyle, improper excessive dietary intakes, psychosocial stress and obesity/adiposity) are similar in the two diseases while microlevel vascular factors are common. Mechanistic features unique to type 2 diabetes are vascular effects of hyperglycemia, diabetic dyslipidemia (elevated and/or dysfunctional triglycerides, low density lipoproteins and high density lipoproteins) as well as chronic inflammatory response to hyperglycemia and abnormal adipocytes. Further research to elucidate mechanisms of premature diabetes related vascular disease, that is unique to India, is required.

BACKGROUND

Coronary heart disease (CHD) and diabetes are epidemic in India. The Million Death Study reported that in years 2001-2003 cardiovascular diseases were the major causes of deaths in India. Of the more than 10.5 million deaths that occur annually, proportionate mortality from these diseases is 18% (males 20%, females 17%) (Figure 1). This corresponds to cardiovascular diseases causing 1.8 million deaths annually. In adults aged 25-69 years cardiovascular diseases cause more than 25% of deaths, most of them premature. Two thirds of cardiovascular deaths are due to CHD while the rest are due to cerebrovascular diseases and others.

Proximate CHD risk factors include dyslipidemias, high blood pressure, diabetes, obesity, and smoking. Lifestyle factors are sedentariness, dietary indiscretion and psychosocial stress. The underlying societal determinants include social changes of rapid urbanization and social and economic consequences of affluence. Genetic factors could be important. Hospital-based studies and case-control studies demonstrate that diabetes is an important cardiovascular risk factor. The INTERHEART study showed that population attributable risk of acute myocardial infarction due to known diabetes was 33%, implying that it is a major factor of risk. When evaluated by biochemical investigations it has been reported that almost 50% of Indians with CHD have diabetes and more than 70% have some form of glucose intolerance.

Type 2 diabetes and associated multiple metabolic abnormalities are increasing in India and studies suggest that it is an important cardiovascular risk factor. Here we review epidemiology of causes of death in diabetes, highlight dual epidemics of type 2 diabetes and CHD in India and detail mechanistic issues causing increased cardiovascular risk in diabetes.

CORONARY DISEASE IS THE MAJOR CAUSE OF DEATH IN DIABETES

Diabetes mellitus causes significant premature mortality. Major causes of death in diabetes are premature cardiovascular disease including CHD and strokes, cancers, renal failure, and acute
and chronic infections. Epidemiological studies in USA and Europe report on causes of morbidity and mortality in type 2 diabetes. Kleinman et al analysed causes of death in a nationally representative US sample and reported that over a 9-year follow-up period relative risk of death in subjects with diabetes as compared to non-diabetics was 2.3 for men and 2.0 for women. 75% of excess deaths in men and 57% in women were due to cardiovascular disease. Data from US National Centre of Health Statistics reported that 40% of deaths in subjects with type 2 diabetes were directly attributed to CHD and 22% were due to other heart diseases such as heart failure. In India discordant results are reported. Studies from North India reported that infections were the major cause of death in hospitalised patients with diabetes while a population based study from South India reported that cardiovascular diseases especially CHD is the largest contributor to deaths.

The prospective AusDiab epidemiological study reported increasing all cause as well as cardiovascular mortality with successively increasing degree of glycemia in Australia. In this study of 10,428 subjects it was observed that over a median follow-up period of 5.2 years, when compared with subjects with normal glucose tolerance, successively increasing levels of glycemia categorized into impaired glucose tolerance, impaired fasting glucose, newly diagnosed diabetes or known diabetes were associated with increasing all-cause as well as cardiovascular mortality (Figure 2). This correlates well with increasing cardiovascular risk with increasing degree of glycemia in population based subjects in India. Framingham Heart Study prospectively reported causes of deaths in type 2 diabetes and reported that cardiovascular diseases were the most important causes of death in diabetes. Over a 7-year follow up it was reported that the risk of cardiovascular death in diabetes was similar to those with previous myocardial infarction. Diabetes is now considered a cardiovascular disease equivalent by the UN National Cholesterol Education Program.

**TYPE 2 DIABETES AND CHD IN INDIA**

In India, there is joint epidemic of type 2 diabetes and CHD. Increasing longevity, greater per capita consumption of dietary calories and fats and the adiposity epidemic combined with rapidly changing socioeconomic status of the Indian population along with rapid urbanization is fuelling this joint epidemic. Epidemiological studies in urban and rural populations performed over the last 50 years have clearly shown increase in prevalence of diabetes as well as CHD in rural and urban populations (Figure 3). The prevalence of type 2 diabetes has increased from less than 1% in rural and 1.5% in urban areas in 1960’s to 6-8% in rural and 10-15% in urban populations currently. The prevalence of CHD has increased from less than 1% in rural populations to 4-5% presently and in urban locations from 1-2% in 1960’s to 9-12% presently. CHD is multifactorial in origin with major factors being sedentary lifestyle, psychosocial stress, dietary factors, smoking, obesity, hypertension, diabetes and lipid abnormalities. Type 2 diabetes risk factors are also similar and sedentary lifestyle, psychosocial stress, dietary factors, and obesity are of major importance.

The cause and effect relationship between diabetes and atherosclerosis is controversial. Both begin from similar abnormal lifestyles and lead to similar end-stage disease in form of widespread blockages of large and small vessels. Atherosclerosis affects predominantly large and medium sized vessels while diabetes affects all types of arteries. The current consensus if that type 2 diabetes occurs earlier and leads to coronary atherosclerosis in a majority of patients. Several mechanisms are likely to contribute to the accelerated atherosclerosis and increased CHD risk in patients with type 2 diabetes mellitus. The issue is still evolving and discordant results are reported from randomised controlled clinical trials, prospective epidemiological investigations and basic scientific studies. Basic mechanistic studies have high relevance to present clinical controversies to understand and address cardiovascular disease risk in people with
Coronary Heart Disease in Type 2 Diabetes: Epidemiology and Mechanisms

Mechanisms for Accelerated Coronary Atherosclerosis in Diabetes

Multiple hypotheses exist to explain the occurrence of premature coronary atherosclerosis in diabetes, but the consensus is that it is multifactorial. Important factors include dyslipidemia, hypertension, hypercoagulability, poor glycemic control, smoking, obesity, and lack of physical activity. Of these, the factors that appear mechanistically most important are (i) hyperglycaemia affecting the vessel wall, (ii) diabetic dyslipidaemia, (iii) hyperglycaemia versus dyslipidaemia, and (iv) chronic subclinical inflammation in the vessel wall.18

Hyperglycaemia and Vessel Wall

Although a consistent association between glycaemic control and cardiovascular disease has been noted in epidemiological studies, the effect of tight glycaemic control did not seem to reduce the cardiovascular risk in clinical trials. Intensive glycaemic control in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study was stopped because of an increase in the number of cardiovascular deaths. The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicro NNR) study on the other hand reported mortality benefits of good glycaemic control for cardiovascular disease events and mortality.20 The VADT (Veterans Administration Diabetes Trial) also reported that tight glycaemic control prevents more events as compared to usual control.21 A large meta-analysis of multiple studies recently reported effectiveness of tight glycaemic control for cardiovascular risk reduction and concluded that optimum methods to achieve this need to be established.22

Results of basic studies in vitro, in animal models, and in patients with diabetes mellitus suggest several mechanisms by which hyperglycaemia might affect atherogenesis at the level of the artery wall.21,22 Firstly, high glucose concentrations can activate nuclear factor kB (NF-kB), which in turn can increase the expression of various genes in the endothelial cells, monocyte-derived macrophages, and vascular smooth-muscle cells. Secondly, advanced glycation end-products (AGEs) including protein cross-links, fluorophors, and other low molecular-weight residues are formed by sustained exposure of proteins and lipids to high concentrations of glucose, which can generate reactive oxygen species. Ligation of AGES to specific cell-surface receptors can regulate gene expression in vessel-wall cells. Thirdly, glucose also increases oxidative stress, which has several possible harmful effects on the artery wall, e.g., auto-oxidation of glucose leads to the formation of several reactive oxygen species, such as the superoxide anion, which can promote LDL oxidation in vitro. And fourthly, indirect observational evidence suggests that lipoprotein oxidation might be increased in patients with type 2 diabetes and is related to glycaemic control. On the other hand, absence of highly specific markers in collagen, plasma, or urine from individuals with diabetes does not support a generalised increase in oxidative stress in diabetes.24

Glycoxidation reactions are thought to contribute to macrovascular disease in diabetes by damaging tissues in the local microenvironment of the arterial wall.25 The pathways leading to these reactions include the generation of superoxide in the mitochondria, NADPH generation by monocyte-derived macrophages, or a redox-sensitive mechanism that generates hydroxyl radicals.

Postprandial hyperglycaemia as an important index of glycaemic exposure and potential oxidative stress has had a resurgence in interest.26 24 h excretion of 8-iso-prostaglandin F2, an indicator of free radical production derived from arachidonic acid in cell membranes was increased in patients with diabetes compared with that in non-diabetic controls. The concentrations of this prostaglandin were highest in patients with the greatest glycaemic variability. Moreover, this variability was a strong predictor of total free radical production, whereas postprandial blood glucose concentrations were not. Further studies are needed to assess the importance of oxidative stress that results from glycaemic variability.

Diabetic Dyslipidaemia

Diabetic dyslipidaemia is strongly related to atherosclerosis.18 Even though patients with type 2 diabetes might not have substantially increased concentrations of LDL cholesterol compared with matched individuals without diabetes, a cornerstone of the management of cardiovascular disease risk in diabetes is the use of LDL cholesterol lowering drugs, i.e., statins.24 These drugs generally reduce cardiovascular disease events by 25-50% but the excess residual cardiovascular disease risk remains for treated patients with diabetes compared with those without diabetes.33 Some of this residual risk could be attributed to lipoprotein abnormalities in patients with type 2 diabetes that are not adequately managed by statin treatment.28 Dyslipidaemia of type 2 diabetes is also characterised by reduced HDL-cholesterol concentrations, increased triglyceride-rich lipoprotein concentrations, and abnormalities in the composition of HDL, LDL, and triglyceride-rich lipoprotein particles (Table 1).

<table>
<thead>
<tr>
<th>Table 1: Lipid abnormalities in type 2 diabetes</th>
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<tr>
<td>Triglyceride rich lipoproteins</td>
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<td>LDL cholesterol</td>
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LDL cholesterol: Increased postprandial concentrations, Triglyceride enriched and cholesterol enriched particles.

HDL cholesterol: Small dense particles.

Triglyceride: Increased postprandial concentrations.

VLDL, metabolites of VLDL, and chylomicron remnants.18 The
role of these lipoproteins in diabetic atherosclerosis remains controversial. Triglyceride concentrations vary inversely with HDL-cholesterol concentrations, confounding interpretations related to increases in concentrations of triglyceride-rich lipoproteins to atherosclerosis. Postprandial triglyceride concentrations might be a better predictor of cardiovascular disease events than fasting triglyceride concentrations, independently of HDL cholesterol concentrations. Triglyceride-rich lipoproteins enhance the proinflammatory phenotype of endothelial cells and macrophages and produce apoptosis in endothelial cells. They increase expression of tumour necrosis factor α (TNFα) and adhesion receptors in macrophages, resulting in increased adherence of monocytes and monocyte-derived macrophages to endothelial cells. Apolipoprotein CIII, a component of triglyceride-rich lipoproteins and an inhibitor of lipoprotein lipase, increases adhesion of monocyctic cells to endothelial cells.

**Low Density Lipoprotein (LDL):**

Patients with type 2 diabetes might not have substantially higher concentrations of LDL cholesterol than matched individuals without diabetes, but for any LDL-cholesterol concentration, those with diabetes generally have an increase in LDL particles because small, dense lipid-poor LDL particles accumulate in the circulation. An increase in the number of LDL particles in diabetes can be treated by statins. However, a separate issue is whether or not small, dense LDL particles are inherently more atherogenic on a per-particle basis than the larger buoyant particles. An increased atherogenicity of small, dense LDL particles is supported by results of in-vitro studies, showing that small LDL particles rapidly enter the arterial wall and can be toxic to endothelial cells, cause greater production of procoagulant factors, be oxidised more readily, and be more readily immobilised by proteoglycans present in the arterial wall than can the large buoyant particles. How these in-vitro results translate to the in-vivo milieu, however, remains unclear. Results from studies of healthy individuals and those with CHD showed that both large and small LDL particles are related to atherosclerosis and cardiovascular disease.

**High Density Lipoprotein (HDL):**

Individuals with type 2 diabetes mellitus have reduced HDL cholesterol and circulating apolipoprotein A1, the major apolipoprotein in HDL cholesterol. Abnormalities in the size and composition of the HDL particle have also been noted in diabetic patients. HDL and apolipoprotein A1 remove excess cholesterol from atherosclerotic plaque cells, and their reduced concentrations in diabetes would be expected to have a detrimental effect on cholesterol content in vessel walls. The cell type of most interest is the monocyte-derived macrophage because cholesterol-ester-engorged macrophages (foam cells) are hallmarks of the atherosclerotic plaque. Removal of cholesterol from macrophages is thought to be an important first step in the process of reverse cholesterol transport, and might be important for the prevention of progression and for regression of atherosclerotic plaques. The HDL particle and its apolipoprotein-A1 component might act through distinct cellular cholesterol transporters for removal of cholesterol from cells. HDL has anti-inflammatory and antioxidant properties in cells of the vessel wall.

In addition to changes in HDL-cholesterol and apolipoprotein-A1 concentrations, patients with type 2 diabetes have changes in HDL composition. HDL is perhaps the most heterogeneous and complex of all lipoprotein particles, and changes in its composition might affect HDL atheroprotective properties. Changes in the content of many proteins associated with HDL, for example paroxonase (opposes oxidation of lipoprotein lipid), might change its atheroprotective properties. Compositional abnormalities of HDL isolated from patients with type 2 diabetes have been linked to impaired antiatherogenic properties. Cholesterol-ester transfer protein inhibition with torcetrapib did not protect against cardiovascular disease events, underscoring the notion that HDL-particle composition might be more important than HDL-cholesterol concentrations for reduction of cardiovascular disease risk.

**Hyperglycemia versus Dyslipidemia**

The roles of hyperglycaemia and hyperlipidaemia in atherogenesis have been difficult to separate. Hyperlipidaemia is usually exacerbated by the onset of hyperglycaemia, e.g., in mouse models of LDL-receptor deficiency and apolipoprotein-E deficiency, thereby confounding the effect of hyperglycaemia. However, in two animal models, hyperglycaemia seems to have an independent role. First, fat-fed diabetic pigs had more atherosclerosis than equally dyslipidaemic fat-fed animals without diabetes. Second, consumption of a cholesterol-free diet by LDL-receptor-deficient mice with a novel form of diabetes induced by a β-cell-directed viral antigen resulted in hyperglycaemia without changes in lipids and lipoproteins. Hyperglycaemia was associated with lesion initiation. Addition of increasing amounts of dietary cholesterol led to dyslipidaemia, which was the major factor in atherosclerosis progression, independent of hyperglycaemia.

**Chronic Vessel Wall Inflammation:**

Evidence ranging from pathological studies in people to animal models has established the role of inflammatory cells (such as macrophages and T lymphocytes) and inflammatory mechanisms (such as cytokine release) in the pathogenesis of atherosclerosis. Because type 2 diabetes and atherosclerosis are chronic conditions that take decades to arise, the cause and effect are difficult to discern. Inflammation is implicated in the pathogenesis of type 2 diabetes and atherosclerosis. Since diabetes promotes atherosclerosis and increases cardiovascular events, a distinction might exist between inflammation that fosters diabetes and inflammation that arises after the type 2 diabetes and promotes atherosclerosis directly. Most of the known inflammatory mechanisms seem to be implicated in the atherosclerosis seen in prediabetic and non-diabetic states. Although the evidence implicating inflammation in atherosclerosis and type 2 diabetes is wide-ranging, a specific mechanism or an integrated framework
Table 2: Guidelines to improve diabetes prevention and management in India

| Primary prevention | Improving physical activity and ameliorating sedentary lifestyles.  
| Dietary moderation.  
| Prevention and reduction of adiposity and obesity.  
| Improvement of medical education.  |
|---------------------|-------------------------------------------------------------|
| Diabetes management | Diabetes management has to move away from the specialist clinic into primary care.  
| Simple management algorithms need to be developed.  
| Model of chronic care at primary care should be developed in India and other developing countries.  
| Quality outcomes framework (QOF) initiative by NHS in a useful, result-based model.  
| Involvement of nurse-practitioner, diabetes nurse, social workers, educators, needed.  
| Specialist services to deal with its complications need novel approaches.  |

has not been identified to explain precisely why patients with diabetes are at increased risk of inflammation or atherosclerosis.

Mechanisms of inflammation:

The endothelium, as the cellular interface between the circulation and hyperglycaemia and dyslipidaemia that characterise type 2 diabetes mellitus, responds to hyperglycaemia and dyslipidaemia by showing an inflammatory response. Most of the responses induced in atherosclerosis are common to both diabetic and non-diabetic atherosclerosis. Classic proatherosclerotic endothelial responses such as adhesion-molecule expression, secretion of chemokines, and coagulation proteins (plasminogen activator inhibitor 1, total plasminogen activator, and tissue factor), and release of vasoactive mediators (endothelial nitric oxide and bradykinin) are induced or regulated by inflammatory stimuli in diabetes models in vitro or in vivo, or both. Macrophages directly respond to the common abnormalities in type 2 diabetes—glucose, free fatty acids, and hypertriglyceridaemia—by augmentation of the inflammatory responses. Several stimuli and cellular pathways are implicated in the effects of macrophages, including increased foam-cell formation, release of matrix metalloproteinases, and secretion of growth factors and cytokines. These effects emphasise the important link between insulin resistance, inflammation, and atherosclerosis. The available data suggest cellular responses to injury, inflammation, and metabolism might converge on control points that are important in atherogenesis. A central regulator of inflammation is NF-κB, a transcriptional complex activated by various stimuli, including cytokines, oxidised LDL, lipopolysaccharide, and oxidative stress. Adipose tissue in adipose tissue might contribute to abnormal metabolism and atherosclerosis in type 2 diabetes. Oxidative stress, endoplasmic reticulum stress, and NF-κB activation pathways also operate in adipocytes. Oxidative stress and inflammation in adipose tissue can be exacerbated by hyperglycaemia. Fatty acids released from adipose tissue may signal to macrophages through pathways that involve toll-like receptors, leading to NF-κB activation. Excess lipid accumulation in other tissues, skeletal muscle and the liver, might modulate inflammation, contributing to insulin resistance and atherosclerosis. Increased concentrations of inflammatory cytokines released from visceral fat in diabetes and obesity can act directly on the vessel wall to increase the circulating concentrations of proinflammatory molecules such as C-reactive protein and serum amyloid A. C-reactive protein might directly amplify injury at the vessel wall and serum amyloid A unfavourably modifies the composition and function of HDL. Several adipocyte-specific mediators have been implicated in the inflammation contributing to insulin resistance and atherosclerosis. Leptin is an adipocyte-specific signal that seems to exert systemic proinflammatory effects. Adiponectin restricts inflammatory and atherosclerotic responses. Adiponectin concentrations are reduced in obesity and diabetes and the treatment of apolipoprotein-e-deficient mice with an adiponectin-expressing adenovirus has proven to reduce atherosclerotic plaque formation. Adiponectin is present at higher concentrations in the subcutaneous fat adipocytes than in visceral fat adipocytes, one of many examples that suggest both depot-specific differences in fat and increased pathogenicity from visceral fat.

CONCLUSIONS

Coronary atherosclerotic vascular disease is the major cause of mortality and morbidity in patients with type 2 diabetes. More than 60% of patients with type 2 diabetes die of coronary heart disease, conversely type 2 diabetes is a major cardiovascular risk factor and in India more than 70% patients with coronary heart disease have diabetes or glucose intolerance. There are macrolevel as well as microlevel mechanisms linking the two diseases. At a macrolevel the sociological (rapid urbanization, rapid affluence), demographic (increased aging) and epidemiological factors (sedentary lifestyle, improper excessive dietary intakes, psychosocial stress and obesity/adiposity) are similar in the two diseases. At the microlevel vascular factors such as endothelial dysfunction, dyslipidemia and inflammation are common. Mechanistic features unique to type 2 diabetes are vascular effects of hyperglycaemia, diabetic dyslipidemia (elevated and/or dysfunctional triglycerides, low density lipoproteins and high density lipoproteins) as well as chronic inflammatory response to hyperglycaemia and abnormal adipocytes. Further research to elucidate mechanisms of diabetes related vascular disease is required.

Actions to prevent occurrence of diabetes in a population and prevent its vascular complications need a concerted public health response. This can be achieved through well tried general-population based, high-risk-population based, and clinic-based high-risk patient focussed approaches. Only then can we ameliorate the
harmful effects of the dual epidemic of premature type 2 diabetes and coronary heart disease in India.

REFERENCES