Diabetes is expanding in pandemic proportions worldwide. Escalation in prevalence of diabetes appears to be more pronounced in developing countries, particularly in India. Presently more than 30 million people are affected by diabetes in India. These numbers are expected to increase to 80.9 million by year 2032. In addition, the emergence of the coronary artery disease (CAD) epidemic in India has added to the economic and health burden of the nation. Various epidemiological studies have consistently reported high prevalence rates of diabetes and CAD among migrant Indians compared to the native population. The risk for CAD among diabetic subjects is greater by a factor of 2 to 4 compared to non-diabetic subjects. The results of the Chennai Urban Population Study (CUPS) revealed that overall 11% of the total population studied had CAD, which is 10 times higher compared that reported 40 years ago. 21.4% of the diabetic subjects and 14.9% of the subjects with impaired glucose tolerance had CAD compared to 9.1% among subjects with normal glucose tolerance. The pathophysiological process of atherosclerosis in diabetic subjects is accelerated by several factors such as hyperglycemia, insulin resistance, abnormal lipid profile, oxidative modification of lipoproteins, increased blood pressure, altered rate of fibrinolysis etc. The article focuses on the role of traditional and newer cardiovascular risk factors in association with diabetes.

**KEY WORDS:** Coronary Artery Disease, Diabetes, Lipoprotein(a), Homocysteine, Fibrinogen, Insulin Resistance Syndrome.

**DIABETES AND CAD**

Diabetes mellitus is a disorder characterized by hyperglycemia and occurs due to impaired insulin secretion and / or impaired insulin sensitivity. Though diabetes mellitus is a metabolic disease, it is also considered as a vascular disease. Affection of the medium sized blood vessels leads to coronary artery disease (CAD), peripheral vascular disease (PVD) and cerebrovascular disease (CVD). Indeed, CAD accounts for more than 50% of the mortality among type 2 diabetic subjects. All the manifestations of CAD are at least two fold more common in patients with diabetes than in non diabetic individuals (1, 2). Conversely, the prevalence of diabetes among subjects with CAD is approximately 20%. Although a considerable decline in the incidence of CAD among the general population has been shown in western countries, there has been no decrease in CAD mortality among diabetic subjects (3, 4). With the recent statistics pointing out to a marked increase in diabetes worldwide (5), one can anticipate rising trends in prevalence of CAD associated with diabetes.

**PREVALENCE OF DIABETES AND CAD IN INDIANS**

According to the recent statistical reports from the World Health Organization, [WHO] India leads the world with the largest number of diabetic subjects (5). Studies on native Indian population have confirmed that during last 30 years, the prevalence of diabetes has risen markedly (6, 7). The prevalence of diabetes among urban Indians in 1970s was 2.1% (8), in 1990s it was 8.2% (9) and this has now risen to 12.1% (10).

The Global Disease Burden Study concluded that CAD mortality in the developing countries in 1990 to be over 9 million, of which India contributed to 2.4 million deaths, which accounts for over 25% of the all deaths reported in India [11]. Furthermore, it is also projected that in India cardiovascular disease would account for majority of the disability adjusted loss of years [DALY’s] in the future (12). According to the World Bank figures, overall cardiovascular mortality in Indians has been projected to rise by 103% in men and 90% in women between 1985 and 2015 (13). Data from the native Indian population, in early 60’s revealed that the prevalence of heart disease was 1.05% [14] and this has increased markedly and
currently ranges from 7.6 – 14.3% (Table 1) (14-23). In the rural population, the prevalence of heart disease has increased from 2.0% in 1974 to 3.8% in 1994, representing a two fold increase in the last 20 years (24, 25).

Table 1: Data on Prevalence of CAD from Various States of India from 1990

<table>
<thead>
<tr>
<th>Reference</th>
<th>State</th>
<th>Sample size (age in years)</th>
<th>Year</th>
<th>Prevalence of CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padmanavathy (15)</td>
<td>Uttar Pradesh</td>
<td>1642 (&gt;20)</td>
<td>1959</td>
<td>1.0%</td>
</tr>
<tr>
<td>Sarvotham et al (16)</td>
<td>Haryana</td>
<td>1331 (&gt;30)</td>
<td>1968</td>
<td>6.6%</td>
</tr>
<tr>
<td>Gupta et al (17)</td>
<td>Haryana</td>
<td>1504 (&gt;30)</td>
<td>1975</td>
<td>4.5%</td>
</tr>
<tr>
<td>Chaddha et al (15)</td>
<td>New Delhi</td>
<td>13,723 (25-64)</td>
<td>1990</td>
<td>9.7%</td>
</tr>
<tr>
<td>Begom et al (16)</td>
<td>Kerala</td>
<td>480 (26-65)</td>
<td>1995</td>
<td>13.9%</td>
</tr>
<tr>
<td>Singh et al (17)</td>
<td>Uttar Pradesh</td>
<td>152 (26-65)</td>
<td>1995</td>
<td>8.6%</td>
</tr>
<tr>
<td>Gupta et al (18)</td>
<td>Rajasthan</td>
<td>2212 (&gt;20)</td>
<td>1995</td>
<td>7.6%</td>
</tr>
<tr>
<td>Ramachandran et al (19)</td>
<td>Tamil Nadu</td>
<td>953 (&gt;40)</td>
<td>1998</td>
<td>14.3%</td>
</tr>
<tr>
<td>Mohan et al (20)</td>
<td>Tamil Nadu</td>
<td>1175 (&gt;20)</td>
<td>2000</td>
<td>11.0%</td>
</tr>
<tr>
<td>Gupta et al (21)</td>
<td>Rajasthan</td>
<td>1123 (&gt;20)</td>
<td>2002</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

Chennai Urban Population Study

The Chennai Urban Population Study (CUPS) is a population-based study involving two residential areas representing the lower and middle-income group in Chennai in South India. All individuals aged greater than 20 years living in these two colonies were requested to participate in this study. The study had an overall response rate of 90.2%. The study subjects were categorized as normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or diabetes based on oral glucose tolerance test (OGTT). CAD was diagnosed using medical history and Minnesota coding of resting 12 lead ECGs (26–28).

The study results revealed the overall CAD prevalence to be 11% in the total population while in the age standardized figure was 9%. 1.2% patients had a documented myocardial infarction, 1.3% had Q wave changes, 1.5% had ST segment and 7.0% had T wave abnormalities (22). The overall prevalence of 11.0% is ten times higher than that reported 40 years ago (29). The prevalence of diabetes in this study population was 12% and an additional 5.9% of subjects had Glucose Intolerance (30). The prevalence of CAD was higher among diabetic subjects. 21.4% (known diabetes - 25.3%, newly diagnosed diabetes – 13.1%) of the diabetic subjects had CAD compared to 14.9% among subjects with impaired glucose tolerance (IGT) and 9.1% among subjects with normal glucose tolerance (22).

PRECLINICAL ATHEROSCLEROTIC MARKERS

The high risk for CAD among diabetic subjects is confirmed by assessing several preclinical atherosclerotic markers, in both diabetic and non diabetic subjects from the CUPS population. In the CUPS, pre-clinical atherosclerotic markers like early structural changes - carotid intimal medial thickness and early functional changes like endothelial dysfunction and arterial stiffness were studied. The mean IMT values among diabetic subjects were significantly higher (0.95 ± 0.31mm) compared to normal subjects (0.74 ± 0.14mm) (p<0.001) (26). Further, carotid atherosclerosis defined as IMT >1.1mm was significantly higher in diabetic subjects [20%] compared to non-diabetic subjects [1%] (31).

Of the two functional markers assessed, endothelial function which was assessed by flow mediated dilatation, decreased significantly in diabetic subjects compared to non-diabetic subjects (32). Arterial stiffness was studied using pulse wave analysis and was found to markedly increased in diabetic subjects [Figure 1] (32). These data indicate that diabetic subjects are more prone to atherosclerotic changes compared to non-diabetic subjects at a younger age.

CARDIOVASCULAR RISK FACTORS IN DIABETIC SUBJECTS
Diabetes mellitus and CAD share many common risk factors. According to Reaven (33) diabetes and CAD are constituents of the metabolic syndrome in which insulin resistance plays a contributory role. There is a clustering of several metabolic disorders like dyslipidemia, hypertension, hyperglycemia and central abdominal obesity [Figure 2]. This cluster has been shown to predict death in type 2 diabetic subjects (34, 35). In addition a number of other factors for CAD such as atherothrombotic factors, fibrinolytic factors, coagulation factors and inflammatory markers have also been described in diabetic patients.

Figure 2 : Interlink of Cardiovascular Risk Factors

**Hyperglycemia and CAD**

Increase in plasma glucose levels have long been recognized as a risk factor for CAD. In fact plasma glucose has been shown to have a continuous gradient relationship with CAD both in the diabetic range and in the non-diabetic range. In the CUPS study, the prevalence of CAD increased with increase in fasting plasma glucose even among non-diabetic subjects. The odds ratio for CAD increased with increase in quartiles of fasting plasma glucose and 2 hr post glucose load plasma glucose indicating a strong association of plasma glucose levels with CAD (29).

**Hypertension and CAD**

Studies have shown that an increase by 5 mm of Hg is associated with 34% increase in risk for cardiovascular disease (36). The overall prevalence of hypertension in CUPS was 22.1% (37). The prevalence of CAD was significantly higher among hypertensive compared to normotensive subjects. The risk for CAD was even higher among subjects who had both diabetes and hypertension [OR-3.13, p=0.004]. Systolic blood pressure and diastolic blood pressure showed a strong correlation with CAD on a univariate analysis in the CUPS study (29).

**Dyslipidemia and CAD**

The term diabetic dyslipidemia refers to a constellation of abnormalities including high triglycerides, low HDL cholesterol and changes in LDL cholesterol qualitatively with an excess of small dense LDL. The excess risk for CAD seen among diabetics is attributed to diabetic dyslipidemia, particularly increase in small dense LDL [38]. A study in Birmingham, USA revealed that migrant Indians have higher small dense LDL compared to their white counterparts (39). In the CUPS study the prevalence of CAD increased with increase in total cholesterol (trend chi square - 26.2, p<0.001), LDL cholesterol (trend chi square - 24.5, p<0.001), triglycerides (trend chi square - 9.96, p=0.002) and total cholesterol / HDL ratio (trend chi square - 6.14, p=0.0132) (22).

**Hypercoagulation and Hypofibrinolysis and CAD**

Diabetes is associated with various abnormalities of the haemostatic and fibrinolytic system. Indeed diabetes is considered to be a hypercoagulable and hypofibrinolytic state. An increased level of fibrinogen and PAI-1 has been indicated by both clinical and epidemiological studies among diabetic subjects (40, 41). Reduced fibrinolysis may predispose diabetic patients to deposit fibrin and this may exacerbate accumulation of LDL, as dyslipidemia is a common phenomenon among these subjects. Recent studies from our centre have shown fibrinogen and PAI-1 levels to be associated with angiographically proven CAD (39) and the relative odds ratios for CAD increased with increase in quartiles of fibrinogen and plasminogen activator inhibitor (42). A very interesting observation was that subjects with diabetes alone (without CAD) also showed elevated levels of tPA and PAI-1 (non-significant). A weak association of PAI-1 with CAD was also shown in another study from South India (43).

**Lipoprotein(a) and CAD**

Lipoprotein(a) is a complex of apolipoprotein (a) and LDL. Lp(a) has a striking homology and common genetic determinants with plasminogen and can competitively inhibit plasminogen activity leading to impaired fibrinolysis (44-46). Lipoprotein (a) has also been implicated in
enhanced oxidation and foam cell formation. In our study we showed that Lp(a) had an independent association with CAD in Type 2 diabetic patients (47). Several other studies have supported this association [42, 43]. Recently we showed that an increase in lipoprotein (a) was associated with increase in carotid intimal medial thickening, a preclinical atherosclerotic marker (48). This suggest that Lp(a) is associated with CAD even at an early stage of atherosclerosis and thus could play a major role in the development of CAD.

**Homocysteine and CAD**

Homocysteine, a sulphur containing amino acid is an atherothrombogenic moiety, which triggers platelet adhesion in cell culture (49, 50) and has been shown to be strongly associated with CAD in several studies. However several studies on its association with CAD among Indians have produced conflicting results (51-53). A cross-sectional study on homocysteine in South Indian diabetic patients and non-diabetic patients with and without CAD found no differences in homocysteine levels (53). As all the Indian studies quoted above were based on small numbers and had measured homocysteine levels in fasting state, prospective larger studies, are required perhaps using methionine loaded homocysteine levels, to look at the association of homocysteine and CAD in Indians.

**Inflammatory markers and CAD**

There is emerging evidences that inflammatory processes and specific immune mechanisms are involved in atherogenesis (54). Atherosclerotic lesions are heavily infiltrated by cellular components associated with inflammation like macrophages and T lymphocytes (55). It has been shown that inflammatory markers predict future cardiovascular events. C-reactive protein (CRP) has recently gained lot of interest (56, 57) and studies have shown CRP to be associated with both diabetes and CAD (58, 59).

**CONCLUSION**

Various risk factors like diabetes, dyslipidemia, hypertension, hypercoagulation, hypofibrinolysis and inflammation are associated with CAD. Some of these factors are modifiable by therapeutic interventions. Most of these factors can be modified by life style modifications like dietary modification, regular physical activity, weight reduction and cessation of smoking. Control of CAD in diabetic patients would however require a multi-pronged approach to reduce the risk of CAD, which includes in addition to life style modifications, tight control of hyperglycemia, blood pressure and hyperlipidemia as shown in the recent Steno – 2 study (60).

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