Diabetes and risk factors for coronary artery disease

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Various epidemiological studies had consistently reported high prevalence rates of diabetes among migrant Indians compared to the native population. The most common and life-threatening disorder that besets type 2 diabetic subjects is coronary artery disease (CAD). The risk for CAD among diabetic subjects is greater by a factor of 2 to 4 compared to non-diabetic subjects. It is well known that Asian Indians have greater risk of developing CAD compared to other ethnic populations. The results of the Chennai Urban Population Study (CUPS) revealed that overall 11% of the total population studied had CAD. This is 10 times higher compared to 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 reason for the enhanced susceptibility for CAD among diabetic subjects is still not clear. However, cardiovascular risk factors have been shown to be more pronounced among diabetic subjects. Further, the diabetes-specific factors like hyperglycaemia, advanced glycation products, altered lipoproteins and hypercoagulation tends to partly explain the high risk for CAD. The review focuses on the traditional and newer cardiovascular risk factors and discusses their contributory role for CAD and their association with diabetes.

The last century has seen a rapid increase in the global prevalence of coronary artery disease (CAD). Estimates from the Global Burden of Disease Study estimate that India faces the greatest burden due to coronary artery disease1. Projection on mortality rates due to CAD in India clearly indicates nearly 100% increase in the rates from 1985 to 2015 (ref. 2). While decline in CAD mortality has been demonstrated among some industrialized countries, the reverse trend appears to be seen in developing countries. This could be explained by the epidemiological transition occurring in these countries3. Indeed, the total number of CAD deaths from China and India equals that of the CAD deaths contributed by all developed countries put together. A marked ethnic diversity has been well documented in the prevalence of CAD with Indians having a higher prevalence of premature CAD4. This has been consistently shown in epidemiological studies on migrant Indians in UK, Trinidad, Singapore and other countries5-8.

Prevalence of CAD among Indians

Despite the well-known occurrence of premature CAD in Indians, there is paucity of population-based data from the Indian subcontinent. In order to investigate the prevalence and risk factors for CAD and diabetes, we took up the Chennai Urban Population Study9-16. 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 the 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 12 lead ECGs. The study results revealed an overall CAD prevalence of 11% in the total population. 1.2% of patients had a documented myocardial infarction, 1.3% had Q wave changes, 1.5% had ST segment and 7.0% had T wave abnormalities. This figure of 11% represents a ten-fold increase in prevalence of CAD in urban India during the last 40 years and the figures are now approaching those reported in migrant Indians5-25 and confirms the findings of an earlier South Indian study (Table 1)25.

The Jaipur Heart Watch-2 study also reported an escalation in the prevalence rates of CAD among North Indians during the past 20 years26. Several other studies have confirmed the increase in heart disease among Indians27-29. A very recent analysis on CAD-related data from India describing the health impact due to acceleration of CAD among Indians, emphasizes the increase in risk factors associated with CAD, particularly diabetes30.
Table 1. Prevalence of CAD in different Indian surveys

<table>
<thead>
<tr>
<th>Reference no.</th>
<th>State, country</th>
<th>Sample size (age cut off in years)</th>
<th>Year</th>
<th>Prevalence of CAD (%)</th>
</tr>
</thead>
</table>
| Native Indians
| 17           | Uttar Pradesh, India     | 1642 (> 20)                     | 1959 | 1.0                   |
| 18           | Haryana, India          | 1331 (> 30)                     | 1968 | 6.6                   |
| 19           | Haryana, India          | 1504 (> 30)                     | 1975 | 4.5                   |
| 20           | New Delhi, India        | 13,723 (25–64)                  | 1990 | 9.7                   |
| 21           | Kerala, India           | 1130 (> 30)                     | 1993 | 7.4                   |
| 22           | Uttar Pradesh, India     | 2212 (≥ 20)                     | 1995 | 7.9                   |
| 25           | Tamil Nadu, India       | 953 (> 40)                      | 1998 | 14.3                  |
| 21           | Tamil Nadu, India       | 1175 (> 20)                     | 2000 | 11.0                  |

Migrant Indians

<table>
<thead>
<tr>
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<th>1421 (40–69)</th>
<th>1993</th>
<th>17</th>
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<tbody>
<tr>
<td>5</td>
<td>Illinois, USA</td>
<td>1688 (≥ 20)</td>
<td>1996</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Diabetes and cardiovascular disease

Over and above the CAD epidemic, the emergence of the diabetes epidemic in India has added to the economic and health burden of the nation. With over 20 million diabetic subjects, India leads the world in the number of individuals with diabetes. The problem with diabetes is that it increases the morbidity and mortality due to the propensity to develop micro and macro angiography. Of all the complications that beset diabetic subjects, the most dangerous and life-threatening is CAD. Diabetic subjects have two or more fold higher risk for CAD compared to non-diabetic population. Despite the wide geographical variation in the prevalence of diabetes and CAD, the association of these two remains strong. Irrespective of the ethnic background, diabetic subjects have been shown to have high risk for CAD compared to the non-diabetic population. Even after adjusting for age, sex and income group the MRFIT study reported three times greater risk for CAD among diabetic men compared to their non-diabetic counterparts. The literature is filled with evidence for the strong association of CAD with diabetes in Europeans. In a clinic-based study, we showed that 17.8% of diabetic subjects had CAD. The prevalence of CAD increased with age and duration of diabetes and nearly 40% of the subjects with diabetes duration more than 20 years had CAD.

The higher prevalence of CAD among diabetic subjects is further substantiated from the results of the Chennai Urban Population Study. 21.4% of the diabetic subjects had CAD compared to 9.1% of subjects with normal glucose tolerance. Indeed the risk for CAD seemed to increase even at the stage of impaired glucose tolerance.

![Figure 1. Prevalence of CAD among south Indians – The Chennai Urban Population Study.](image-url)

Studies on preclinical atherosclerosis

End points of atherosclerosis like coronary artery disease or strokes are late events. In order to prevent these end points, it is important to study early or preclinical atherosclerosis at a stage when there are no clinical signs or symptoms of those complications. With advances in technology it is possible to study both structural changes and functional changes in arteries. Structural changes can be studied by measuring intimal medial thickness (IMT) of the carotid arteries using a high resolution ultrasound machine.

Structural changes: Intimal medial thickness

We examined the carotid intimal medial thickness (IMT) in CUPS in diabetic and non-diabetic subjects. The mean
IMT values among diabetic subjects were higher (0.95 ± 0.31 mm) compared to normal subjects (0.74 ± 0.14 mm) \((P < 0.001)\). The range of IMT values in non-diabetic subjects was 0.5–1.2 mm and in diabetic subjects, 0.4–3.0 mm. Carotid atherosclerosis (defined as IMT > 1.1 mm) was present in 20% of diabetic subjects compared to 1% of non-diabetic subjects\(^{10}\).

We also observed that the diabetic subjects had increased IMT at every age point compared to their non-diabetic counterparts\(^{10}\). Further, the newly diagnosed diabetic subjects had significantly higher IMT values compared to normal subjects \(P = 0.002\), but significantly lower compared to known diabetic subjects \(P = 0.04\). Further analysis of the data revealed that diabetes per se was an important risk factor for increase in IMT\(^{10}\).

**Studies on functional changes in arteries**

We next carried out studies on the functional changes in the artery by measuring two parameters, namely endothelial dysfunction and arterial stiffness. Endothelial dysfunction was measured as flow-mediated dilatation (FMD) of the brachial artery using high resolution B mode ultrasonography. Flow-mediated dilatation (FMD) was found to be reduced in diabetic patients (2.1 ± 2.95%) compared to age and sex-matched non-diabetic subjects (6.64 ± 4.38%), \(P < 0.0001\) (Figure 2)\(^{15}\). We also measured arterial stiffness assessing by the augmentation index of the radial artery by the Sphygmocor machine. Arterial stiffness was found to be significantly greater in diabetic subjects (27.48 ± 7.41%) compared to age and sex matched non-diabetic subjects (19.10 ± 8.19%), \(P < 0.0001\) (Figure 2)\(^{15}\).

More than 80% of all deaths and 75% of all hospitalizations in diabetic patients are due to CAD. Recently a study on atherectomy specimens from diabetic patients revealed increased incidence of thrombus in diabetic patients compared to non-diabetic patients\(^{16}\). Morphology studies of autopsy specimens revealed increased prevalence of myocardial lesions in subjects with diabetes\(^{37}\).

All these studies clearly indicate that these two complex diseases namely diabetes and coronary artery disease have a strong association. However, the underlying mechanisms linking these two diseases still remain an enigma. The questions that still remain unanswered are. Do CAD and diabetes spring from a common soil? Do they occur in series or parallel? Is there a single central phenomenon responsible to explain the events? These unanswered questions become the research priorities of the future.

**Cardiovascular risk factors among diabetic subjects**

Several landmark studies in the west have helped to identify a host of risk factors, which predispose to CAD. Indeed, the risk factor concept is 50 years old and the list of factors keep on increasing with our improved understanding of the disease processes. A list of the currently recognized cardiovascular risk factors is provided in Table 2 and its contribution to CAD is shown in Figure 3. Developing countries, particularly India must carry out studies of the risk factors, which operate in their countries as this provides the basis for prevention. Let us examine some of the well known and some less weak accepted risk factors and their risk in predisposing to CAD with particular reference to studies in Indians.

**Figure 2.** Agewise distribution of arterial stiffness and endothelial dysfunction in diabetic and non-diabetic subjects (The Chennai Urban Population Study\(^{35}\)). Figures in parenthesis denote SD.
Table 2. Cardiovascular risk factors

<table>
<thead>
<tr>
<th>Non-modifiable risk factors</th>
<th>Modifiable risk factors</th>
<th>Newer risk factors</th>
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<tbody>
<tr>
<td>Age</td>
<td>Cigarette smoking, Obesity, Diabetes</td>
<td>Lipoprotein(a), Homocysteine, Plasma fibrinogen</td>
</tr>
<tr>
<td>Male sex</td>
<td>Hypertension, Elevated cholesterol</td>
<td>Tissue plasminogen activator</td>
</tr>
<tr>
<td>Family history</td>
<td>Behavioural risk factors</td>
<td>Plasminogen activator inhibitor-1</td>
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<td></td>
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<td>C-Reactive protein</td>
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<td></td>
<td>Protective factors</td>
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<tr>
<td></td>
<td></td>
<td>Exercise, HDL cholesterol, Stress reduction</td>
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</tbody>
</table>

Hyperglycaemia

In the Chicago Heart Study\textsuperscript{38}, an increased risk for CAD mortality was documented among subjects with asymptomatic hyperglycaemia compared to those with post-load glucose levels less than 160 mg/dl. The DIGAMI study provided direct evidence for the association of hyperglycaemia with CAD, as it showed a significant reduction in the CAD mortality rate by multidose insulin regimen\textsuperscript{39}. The UKPDS study showed a non-significant reduction in myocardial infarction with regard to management of glycaemia\textsuperscript{40}. Further studies have revealed a strong association of CAD with plasma glucose levels even among the non-diabetic subjects\textsuperscript{41}. In the Chennai Urban Population Study, univariate regression analysis revealed both fasting plasma glucose and 2 h plasma glucose levels to be strongly associated with CAD\textsuperscript{43}.

Increased glucose tends to react with proteins, to form, glycosylated proteins. The glycosylated haemoglobin (HbA1c) is considered to be the best indicator of glycaemia. Several studies have associated HbA1c with mortality (all cause and CAD-specific) and have shown an increase in mortality with increase in HbA1c levels\textsuperscript{42}. The glycosylated proteins undergo irreversible changes and form compounds called AGE (advanced glycation end) products. These AGE products hasten aging processes and promote degenerative diseases including Alzheimer’s disease. AGE formation increased in subjects with CAD\textsuperscript{43}.

The hypothesis is that AGE triggers atherosclerotic process by glycosylation of low density lipoproteins, which in turn undergo oxidation to form OX-LDL. The OX-LDL could trigger the expression of adhesion molecules for monocytes and thus lead to formation of foam cells, plaque progression and ultimately to clinical events like myocardial infarction.

Insulin resistance

Increased risk for CAD among diabetic subjects is not fully explained by concomitant elevations in traditional risk factors like raised blood pressure and abnormal lipid pattern. However, these factors have been documented to be accelerated among diabetic subjects.

Insulin resistance, and the compensatory increase in insulin secretion bring about a state of chronically increased insulin and glucose levels in the blood (hyperinsulinemia and hyperglycaemia) and thus is a predecessor for diabetes. Reaven\textsuperscript{44} explored the association of insulin resistance with CAD and suggested that diabetes is a part of the insulin resistance syndrome also called the metabolic syndrome, which includes central body obesity, dyslipidemia, and hypertension.

The prevalence of Insulin Resistance Syndrome (IRS) defined using the European Group of Insulin Resistance (EGIR) criteria was 11.2% among South Indians\textsuperscript{14}. The definition for IRS was insulin resistance calculated using the Homeostasis Assessment, insulin resistance (IR) or HOMA IR > 1.93, which is the 75th percentile of the total population) in combination with at least 2 of the following conditions; hyperglycaemia, hypertension, dyslipidemia or central body obesity\textsuperscript{14}. Earlier studies both on migrant Indians and native Indians have shown high prevalence rates of hyperinsulinemia\textsuperscript{45}, insulin resistance\textsuperscript{46} and other components of metabolic syndrome\textsuperscript{47–52}. Age, body mass index and socioeconomic status had a strong association with insulin resistance syndrome\textsuperscript{14}. Recent studies have also shown low birth weight to be a contributor for insulin resistance among Indians\textsuperscript{23}. It has been hypothesized that...
lower birth weight followed by increased obesity could lead to IRS during adulthood. Hyperinsulinemia has been shown to have a potential role or a contributing role for coronary events in Asian Indians. In addition clustering of risk factors of the insulin resistance syndrome have also been shown among native Indians. The subject of insulin resistance is elegantly reviewed by Anoop Misra in another article in this issue and hence we are not discussing this further.

Hypertension

The mechanisms underlying the link between diabetes and hypertension are subject to substantial speculation and are not yet clearly defined. Peripheral insulin resistance and hyperinsulinemia have been proposed to impair insulin-mediated renal sodium resorption, which may contribute to hypertension. Hyperinsulinemia also results in vascular overactivity due to sympathetic activation. Increased erythrocyte Na+/Li+ counter transport has been reported in insulin resistant state which in turn is associated with hypertension.

The Framingham Heart Study clearly demonstrated the association of hypertension with CAD. High blood pressure accounts for 20 to 25% of all CAD deaths. Subjects with hypertension have a two-fold higher risk of CAD. The overall prevalence of hypertension in CUPS was 21.1%. The prevalence of CAD was significantly higher among hypertensives compared to normotensives (Figure 4). There is a wealth of information on control of hypertension and reduction in incident CAD. With regard to diabetic subjects, the UKPDS study proved beyond doubt that blood pressure control decreased the risk of CAD.

Dyslipidemia

In diabetes, there is a derangement in the metabolism of lipids and fat, which leads to abnormal serum lipid pattern. Dyslipidaemia has long been shown to have a strong relation with CAD. Of the various serum lipids, there is ample evidence for a strong association for cholesterol with CAD. Several intervention studies have clearly shown reduction in CAD mortality by reducing cholesterol levels. However, the association of triglycerides with CAD is still in debate although a recent review substantiates its role as a risk factor for CAD. While CAD patients with high triglyceride levels and other lipid abnormalities may benefit from triglyceride level agents, the recent NCEP guidelines emphasize LDL cholesterol less than 100 mg/dl as the main treatment goal.

In CUPS we found that serum cholesterol, LDL cholesterol and total cholesterol/HDL cholesterol ratio were elevated in those with CAD compared to those without CAD (Table 3). The prevalence of CAD significantly increased with increase in quartiles of total cholesterol (trend $\chi^2 = 26.2, P < 0.001$), triglycerides (trend $\chi^2 = 9.96, P = 0.002$) and LDL cholesterol (trend $\chi^2 = 24.5, P < 0.001$) levels. However, LDL cholesterol had the strongest association with CAD on regression analysis.

Recent studies reveal small dense LDL to be more susceptible to oxidation. Oxidized LDL enhances foam cell formation and this leads to inflammatory and thrombogenic processes. Studies on Europeans have identified small dense LDL to be associated with CAD. Further, subjects with small-dense LDL levels have high triglyceride levels and low levels of HDL. A recent study showed that migrant Asian Indians have an excess of small-dense LDL molecules compared to Europeans and this might be one of the mechanisms contributing to increase in CAD in Indians.

In contrast to LDL cholesterol, HDL cholesterol actually plays a protective role, as it is both antiatherogenic and also prevents peroxidation as it carries enzymes like paraoxanases. It was the Framingham study, which first established low levels of HDL as a risk factor for CAD. Recent studies like the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT) provided direct evidence that raising the HDL cholesterol levels reduces the incidence of fatal and nonfatal myocardial infarction. It has been known for a long time that migrant Indians have low HDL cholesterol levels. This has been recently confirmed in studies in India also.

In CUPS, we found that in face of low HDL cholesterol levels, even a modest elevation of LDL cholesterol becomes a powerful risk factor for CAD. In another clinic-based study of 6,597 diabetic patients, we found isolated serum cholesterol, LDL cholesterol and low HDL cholesterol to be associated with CAD in subjects with Type 2 diabetes.

Newer risk factors for CAD

Despite the long list of traditional and conventional risk factors, 50% of the CAD still remains unexplained. This led researchers to think of novel risk factors, which might contribute to CAD (Table 2). Some of the comparative
However, studies on migrant Indians have suggested that the excess risk for CAD seen among Indians could be partly explained by these risk factors. Some of the newer risk factors are briefly discussed below.

**Lipoprotein(a)**

Lipoprotein(a) is a complex of Apoprotein (a) and LDL. Apoprotein (a) is an atherothrombogenic moiety, which can competitively inhibit plasminogen activity leading to impaired fibrinolysis. Lipoprotein (a) has also been implicated in enhanced oxidation and foam cell formation. Elevated levels of this genetically determined lipoprotein is associated with increased risk for atherosclerosis and CAD. Ethnic variation has been shown in Lipoprotein(a) levels and more specifically with the isoform of apo(a) that determines the risk for CAD. The smaller, the apo(a), the higher are the lipoprotein(a) levels and higher the risk for CAD. Lipoprotein(a) levels above 20mg/dl are reported to be associated with a high risk for CAD.

The association of Lipoprotein(a) with diabetes is not very clear and remains controversial. However, even among diabetic subjects, the association of lipoprotein(a) with CAD remains unaltered. We have recently shown lipoprotein(a) to be an independent risk factor for CAD in Type 2 diabetic patients. Several other studies have supported this association. We also recently showed that increase in lipoprotein (a) is associated with an increase in carotid intimal medial thickening, a subclinical atherosclerotic marker.

**Homocysteine**

Homocysteine, a sulphur-containing amino acid has been shown to be atherothrombogenic. Recent cell culture studies showed that homocysteine triggers platelet adhesion. Migrant Indian studies have shown higher levels of homocysteine compared to the native population. However studies on its association with CAD among native Indians have been consistently negative.

We measured the mean homocysteine values in South Indian diabetic patients and non-diabetic patients with and without CAD and found no differences. However, it must be emphasized that all the Indian studies quoted above were based on small numbers and had measured homocysteine levels in fasting state. Larger studies, perhaps using methionine loaded homocysteine levels, are needed to throw further light on the association of homocysteine and CAD in Indians.

**Coagulation and fibrinolytic factors**

Recent studies have identified defects in coagulation and the fibrinolytic cascade to play a major role in the pathological mechanisms leading to CAD. These two cascades consist of activators and inhibitors which regulate clot formation and vascular potency. Measurement of activators, inactive precursors and inhibitors of this cascade has been considered as indicators of activity of these pathways. Fibrinogen is one of the key elements in this cascade. Fibrinogen has been shown to be associated with enhanced platelet aggregation and smooth muscle cell proliferation. Furthermore, there is a strong association of fibrinogen with blood viscosity and thrombus formation and circulating levels of fibrinogen have been known to have a strong and consistent relationship with CAD. Recent studies on native Indians have clearly shown fibrinogen levels to be strongly associated with angiographically proven CAD and the relative odds ratio for CAD have been shown to be increased with increase in quartiles of fibrinogen (Figure 5). The coagulation system has many inhibitors like antithrombin III, protein S, Protein C and thrombomodulin. All these inhibitors have been shown to be associated with CAD in various studies.

In the fibrinolytic cascade, conversion of plasminogen to plasmin is a crucial step. This is regulated by tissue plasminogen activator (tPA) and urokinase. Both these activators are inhibited by plasminogen activator inhibitor-1 (PAI-1). Cross-sectional studies on various ethnic groups have shown the association of plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator inhibitor-1.
tor (tPA) with CAD. Further, a study in migrant Indians has shown high levels of these factors in Indians compared to other ethnic groups. Native Indian studies on angiographically proven CAD patients showed significantly higher levels of tPA, PAI-1 and fibrinogen compared to subjects without CAD. Patients with CAD were distributed more in the upper tertiles of these risk factors compared to those without CAD. Regression analysis revealed hypertension and fibrinogen as strong risk factors for CAD while PAI-1 showed a weak association with CAD. This study also revealed that these factors are elevated even among subjects with diabetes who had no evidence of CAD. Thus, diabetes per se, appears to be a hypercoagulable state and hence could be directly linked to CAD. Indeed, diabetes is now considered by several workers to be a cardiovascular disease. Further, studies on native Indians have revealed PAI-1 to be one of the factors in the insulin resistance cluster and that it is associated with triglyceride levels.

**Inflammatory markers**

The inflammatory theory of CAD, also known as the immunological hypothesis, is now widely accepted by scientists for explaining the vulnerability of plaque and the occurrence of clinical events. Ridker suggested that the genesis of atherosclerotic plaque is dependent on the interplay of cellular components of the immune system like cytokines, adhesion molecules, lipids, platelets and endothelial cells. In this regard the role of inflammatory markers like C-reactive protein, cytokines like interleukin-6 and adhesion molecules like VCAM, ICAM in CAD have been extensively studied.

C-reactive protein (CRP), an acute phase reactant has long been considered as a classic marker for inflammation. Acute inflammation, infection, or tissue injury induces a marked increase in CRP. As atherosclerosis involves inflammation of the vascular endothelium, CRP levels tend to be raised. Several prospective clinical case control studies in Europeans have identified CRP as a strong, independent risk factor for CAD. With the advent of high sensitive (hs-CRP) assays this risk factor is gaining importance in the field of CAD and atherosclerosis.

Basic research studies have revealed that inflammatory markers are high among subjects with insulin resistance and diabetes. Inflammation is considered to be a part of insulin resistance syndrome and this to some extent explains the high risk for CAD among diabetic subjects. There are, however, very few studies in Indians and this is obviously a fertile field for future research studies.

**Conclusion**

CAD is a multifactorial condition for which diabetes is an important risk factor. Tremendous progress has been made in the understanding of CAD in diabetic patients. However, it is now well recognized that as diabetes itself involves interplay of several risk factors, mere control of hyperglycemia may not be sufficient to prevent CAD in diabetic patients. A multi-pronged approach with reduction in serum lipids, better control of blood pressure, weight reduction, cessation of smoking and probably using aspirin or other antiplatelet therapies would probably be needed to prevent CAD in diabetic subjects. Prospective studies on the relative role and importance of traditional and newer risk factors are urgently needed in Indians within the subcontinent. As several risk factors for diabetes and CAD are common (e.g. obesity, physical inactivity, hyperlipidemia, smoking, insulin resistance, etc.) an active public health policy is urgently needed to reduce the twin epidemics of diabetes and CAD in our country.

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