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Epidemiology of Cardiovascular Disease in Type 2 Diabetes: The Indian Scenario

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Abstract

Noncommunicable diseases, of which coronary artery disease (CAD) and diabetes top the list, have overtaken communicable diseases with respect to overall mortality, even in developing countries like India. High prevalence rates of diabetes and CAD are seen not only in affluent migrant Indians, but also in those living within the subcontinent. Indeed the epidemic of diabetes and CAD is now spreading to the middle- and lower-income groups in India. The risk for CAD is two to four times higher in diabetic subjects, and in Indians, CAD occurs prematurely, i.e., one to two decades earlier than in the West. Thus there is an urgent need for studies on CAD in diabetic and nondiabetic subjects in India.

The Chennai Urban Population Study, a population-based study in Chennai, in South India, showed a prevalence of CAD of 11%, which is 10 times more than what it was in 1970. Clustering of risk factors for CAD such as hyperglycemia, central body obesity, dyslipidemia, and hypertension tends to occur, and interplay of these risk factors could explain the enhanced CAD risk in Indians. Additionally, low-grade inflammation and a possible inherent genetic susceptibility are other contributing factors. Preventive measures such as lifestyle modification with healthy diet, adequate physical activity, and decrease in stress could help prevent the twin epidemics of diabetes and CAD.

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Introduction

Type 2 diabetes is on the verge of becoming a pandemic in India.[1] As type 2 diabetes shares several risk factors in common with coronary artery disease (CAD), such as age, hypertension, dyslipidemia, obesity, physical inactivity, and stress, an increase in the prevalence of diabetes indirectly implicates an escalating risk of CAD as well.[2,3] Diabetic subjects are known to have a two to four times increased CAD risk, and CAD has been reported to occur two to three decades earlier in diabetic subjects as opposed to their nondiabetic counterparts.[2]

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Abbreviations: (AI) augmentation index, [Apo(a)] apolipoprotein (a), (CAD) coronary artery disease, (CRP) C-reactive protein, (CUPS) Chennai Urban Population Study, (CURES) Chennai Urban Rural Epidemiology Study, (EGIR) European Group of Insulin Resistance, (FMD) flow-mediated dilatation, (HDL) high-density lipoprotein, (IGT) impaired glucose tolerance, (IMT) intimal medial thickness, (IRS) insulin resistance syndrome, (LDL) low-density lipoprotein, [Lp(a)] lipoprotein (a), (MI) myocardial infarction, (NCEP) National Cholesterol Education Program, (NGT) normal glucose tolerance, (OR) odds ratio, (OSA) obstructive sleep apnea, (PAI-1) plasminogen activator inhibitor-1, (TNF-α) tumor necrosis factor α, (UKPDS) United Kingdom Prospective Diabetes Study

Keywords: Asian Indians, cardiovascular risk factors, coronary artery disease, South Asians, type 2 diabetes

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The life expectancy of people with diabetes is reduced by nearly eight years due to increased mortality.[4] Coronary artery disease accounts for more than 80% of all deaths and 75% of all hospitalizations in diabetic subjects.[5,6] It is also reported that plaques are more vulnerable to rupture among patients with diabetes.[7]

The association between CAD and diabetes is strong despite the fact that there are wide ethnic and geographic variations in their prevalence. The protective female gender effect is lost in diabetic subjects, and indeed, women with diabetes are possibly more prone to develop CAD than men with diabetes.[8] It was established in the Organization to Assess Strategies for Ischaemic Syndromes study that diabetic subjects without prior CAD had a similar risk of CAD as nondiabetic subjects with prior CAD, with poorer prognosis seen in diabetic subjects than nondiabetic subjects after a clinical event.[5] Diabetes has been categorized as a cardiovascular risk equivalent according to the current National Cholesterol Education Program (NCEP) guidelines.[9] Metabolic abnormalities due to diabetes have been found to predispose to vascular changes, leading to atherosclerotic end points.[10] In addition to cardiovascular risk factors seen in nondiabetic subjects, diabetes-specific cardiovascular risk factors also contribute to CAD in diabetic subjects.

Health Burden Due to Coronary Artery Disease and Diabetes Worldwide

Since 1990, CAD has been the leading cause of death worldwide, and this trend is expected to continue until 2020.[11] Cardiovascular diseases accounted for 30.9% of all deaths in 1998 and 10.3% of disability adjusted life year loss.[11] Most of the developing countries have witnessed a dramatic increase in the prevalence of CAD, while the developed countries have followed a reverse trend.[12] By 2020, 85% of the global cardiovascular disease burden is expected to be borne by developing nations, and the increase in CAD mortality in developing countries between 1990 to 2020 is projected to be 120% in women and 137% in men.[13,14] As these projections are based on conservative figures and changes in demography of the population, the actual numbers of CAD-related deaths would be more alarming if increases in all cardiovascular risk factors are taken into account.

Currently holding the 15th place in the list of causes of death worldwide, diabetes is expected to affect 300 million people globally by the year 2025 compared to 135 million in 1995, according to recent statistics from the World Health Organization.[1] Moreover, the increase in prevalence of diabetes in developing countries is projected to be 170% compared to 42% in developed countries. Thus, developing nations would contribute to more than 75% of the global diabetes burden by the year 2025.

Epidemiology of Coronary Artery Disease in Indians

India is predicted to bear the greatest CAD burden, according to the estimates from the Global Burden of Disease Study.[11] Of the more than 9 million deaths due to CAD in 1990 in developing countries, 2.4 million (25%) occurred in India.[11,14] In the same year, mortality rates in India due to acute myocardial infarction (MI) were 141 per 100,000 in males and 136 per 100,000 in females, which was much higher than in China (66 per 100,000 in males and 69 per 100,000 in females) and Latin American countries (81 per 100,000 in males and 76 per 100,000 in females). The overall cardiovascular mortality in Indians is predicted to rise by 103% in men and 90% in women between 1985 and 2015. A matter of serious concern is that 52% of the CAD deaths in India occurred in people aged below 70 years, while the same was just 22% in developed countries.[14,15]

In 1959, Shaper and Jones demonstrated the predilection to CAD among Asian Indians in Uganda.[16] Later studies from various parts of the world not only confirmed that migrant Indians have much higher prevalence of CAD and CAD mortality rates compared to the host populations of those countries but also showed that Asian Indians develop CAD at least a decade earlier.[17–22] Higher prevalence of cardiovascular disease in South Asians living in Canada as compared to Europeans and Chinese was demonstrated by the Study of Health Assessment and Risk in Ethnic groups study.[22]

Evidence indicates that the prevalence of CAD is rapidly increasing in India, particularly in the urban areas. In the 1970s, prevalence of CAD was 1.0% in urban India.[14] By 1990, the prevalence of CAD reported by Chadha *et al.* in Delhi was 9.7%.[23] Remarkably high prevalence of both CAD and cardiovascular risk factors was also shown in the Jaipur Heart Watch study.[24] A meta-analysis of the CAD prevalence based on the surveys conducted since 1990 suggested that the increase in prevalence of CAD in the urban and rural populations were nine-fold and two-fold, respectively.[25] Thus, in the next 15 years, a phenomenal increase in the prevalence of CAD is expected in India, adding to the health burden due to CAD among Indians.[15,25]

Epidemiology of Diabetes in Indians

There are currently 135 million people with diabetes in the world, and India leads the world with 40.9 million people in diabetes in 2007.[26] Moreover, it is projected that, by the year 2025, 80.9 million will have diabetes in India. The prevalence of diabetes in urban Indians has steadily increased from 2.1% in the 1970s[27] to 8.2% in the 1980s,[28] later climbing to 12–16%.[29,30] Thus the phenomenon of high prevalence of diabetes reported among migrant Asian Indians[31] has now spread to urban India and is rapidly moving to rural areas as well.[32] There is still inadequate population-based data on the prevalence of CAD in India, particularly comparing diabetic and nondiabetic subjects.

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 groups in Chennai in South India.[33] All inhabitants in these two colonies aged above 20 years were requested to participate in the study, and 90.2% responded to the study. The subjects were classified as normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes, based on oral glucose tolerance test. The prevalence of diabetes in this study population was 12%, while that of IGT was 5.9%.[34]

Techniques and Methods Used to Assess CAD and Pre-clinical Atherosclerotic Markers in CUPS

In the CUPS, CAD was diagnosed based on a past history of documented MI or electrocardiogram changes suggestive of ST-segment depression (Minnesota codes 1-1-1 to 1-1-7) or Q-wave changes (Minnesota codes 4-1 to 4-2) or T-wave changes (Minnesota codes 5-1 to 5-3).[35]

Structural and functional preclinical atherosclerotic markers were also assessed in diabetic and nondiabetic subjects in the CUPS population. Carotid intimal medial thickness (IMT) was studied to assess the structural changes in the arteries, and functional changes were assessed by studying endothelial dysfunction by flow-mediated dilatation and arterial stiffness studies.[36–38]

Measurement of the Carotid Intimal Medial Thickness

Measurement of the carotid IMT is being used increasingly as a noninvasive marker of atherosclerosis.[38] In the CUPS, the intimal plus medial thickness of the carotid arteries was determined using a high-resolution B mode ultrasonography system (Logic 400 GE, Milwaukee, WI) having an electrical linear transducer midfrequency of 7.5 MHz. The axial resolution of the system was 0.3 mm. The images were recorded as well as photographed. The scanning was done for an average of 20 min. Intimal medial thickness, as defined earlier,[39] was measured as the distance from the leading edge of the first echogenic line to the second echogenic line. The first echogenic line represents the lumen intimal interface, and the second line is produced by the collagen-containing upper layer of the intimal adventitia. At each longitudinal projection, determinations of IMT were conducted at the side of greatest thickness and at two points 1 cm upstream and 1 cm downstream from the side of greatest thickness, as described previously.[40] The mean of the six IMT measurements (three from the left and three from the right) was used as the representative value for each subject.

Arterial Stiffness Assessment

Arterial stiffness was assessed by measuring the augmentation index (AI) using the Sphygmocor machine (Sphygmocor BPAS–1; PWV Medical, Sydney, Australia). In brief, a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, Texas) was used to flatten but not occlude the right radial artery using gentle pressure. When the two surfaces are flattened, circumferential pressures are equalized and an accurate pressure waveform can be recorded. Data were collected directly into a portable microcomputer. The system software allowed online recording of the peripheral waveform, which was assessed visually to ensure that the best possible recording was obtained and that artifacts from movement were minimized. After 20 sequential waveforms had been acquired, the integral software was used to generate an averaged peripheral and corresponding central waveform that was used for the determination of the AI. The AI was defined as the difference between the first and second peaks of the central arterial waveform, expressed as a percentage of the pulse pressure.[39]

Endothelial Dysfunction

Endothelial dysfunction was measured as flow-mediated dilatation (FMD), and FMD of the brachial artery was determined using a high-resolution B-mode ultrasonographic system (Logic 400 GE) with an electrical linear transducer midfrequency of 7.5 MHz, using the technique described by Celermajer and associates.[38] Briefly, each subject was requested to lie at rest for more than

10 min before the procedure began, and the first scan at rest was then taken. This was followed by inflation of the pneumatic tourniquet of the standard sphygmomanometer (Diamond BP Apparatus) placed around the forearm to a pressure of 300 mm Hg followed by deflation after 4.5 min. The second scan was taken 30 s before and 90 s after cuff deflation. Fifteen minutes was then allowed for vessel recovery, and a further scan at rest was then recorded. Sublingual glyceryl trinitrate spray (400 μg) was administered, and 3 to 4 min later, the last scan was performed. Electrocardiography was monitored continuously throughout the study. Flow-mediated dilatation was calculated using the following ratio: diameter of brachial artery after cuff deflation to the diameter measured at rest.[38]

In the CUPS study, all three preclinical atherosclerotic markers were assessed on the same day on the right side (right common carotid artery, right brachial artery, and right radial artery).

Coronary Artery Disease in Diabetic and Nondiabetic Subjects in the Chennai Urban Population Study

The prevalence of CAD in the CUPS study was 11% in the total population, with 1.2% patients having had a MI, 1.3% with Q-wave changes, 1.5% with ST-segment changes, and 7.0% with T-wave abnormalities.[41,42] This 11% represents a 10-fold increase in CAD prevalence in urban India since 1970,[41,43] now approaching those reported in migrant Indians. In the same study, the prevalence of CAD among diabetic subjects was 21.4% (known diabetes, 25.3%, and newly diagnosed diabetes, 13.1%), which was much higher than the figure of 14.9% among subjects with IGT and 9.1% among those with NGT (**Table 1**).[41] Prevalence of known MI was three times higher in diabetic subjects. However, this study showed that the risk for CAD increased even at the stage of IGT itself.

Table 1.
Prevalence of Coronary Artery Disease in South Indian Subjects With and Without Glucose Intolerance[41]

	Subjects		
	NGT	IGT	Diabetes
Documented MI (%)	0.9%	—	3.4%
Overall Q waves (%)	1.2%	1.4%	8.2%
ST-segment depression (%)	1.1%	5.4%	2.8%
T-wave abnormalities (%)	6.6%	8.1%	9.0%
Total CAD prevalence (%)	9.1%	14.9%	21.4%

Preclinical Atherosclerotic Markers in Diabetic and Nondiabetic Subjects in the Chennai Urban Population Study

In the CUPS, the mean IMT values among diabetic subjects were significantly higher (0.95 ± 0.31 mm) compared to normal subjects (0.74 ± 0.14 mm) ($p < .001$). The range of IMT values in nondiabetic subjects was 0.5–1.2 mm, whereas it was 0.4–3.0 mm in patients with diabetes. An IMT value ≥ 1.1 mm was used as a cut off for defining carotid atherosclerosis, and using this definition, 20% of diabetic subjects had carotid atherosclerosis compared to 1% of nondiabetic subjects.[44]

Endothelial dysfunction, measured as FMD, was found to be reduced in diabetes patients compared to age- and sex-matched nondiabetic subjects.[45] Arterial stiffness was also found to be significantly greater among diabetic subjects compared to age- and sex-matched nondiabetic subjects. Pearson correlation analysis of AI and FMD was done with the risk factors for CAD, which revealed age, fasting plasma glucose, and glycated hemoglobin to be positively associated with AI and negatively associated with FMD. These studies confirm that Asian Indian diabetic subjects have an increased tendency to develop premature atherosclerosis compared to their nondiabetic counterparts.

Diabetes–Coronary Artery Disease Link

The identified risk factors for CAD include aging, smoking, and a family history of CAD. Type 2 diabetes is a part of the insulin resistance cluster or metabolic syndrome, which is a combination of hyperglycemia, central body obesity, dyslipidemia, and hypertension (**Figure 1**).[41] Each of these can contribute independently to the CAD risk or may cluster to increase the risk (**Figure 2**).[46] The role of some CAD risk factors are discussed here, particularly in relation to studies from India.

Plasma Glucose Levels and Coronary Artery Disease

Multiple biochemical alterations have been reported in diabetes, and several metabolic pathways seem to be involved in glucose toxicity, with a possible redundancy in their mechanisms.[47] Insulin deficiency and hyperglycemia enhance glucose metabolism through multiple pathways, including the polyol pathway, advanced glycation end products, protein kinase C, and hexosamine pathway (**Figure 3**).[48] Increased plasma glucose concentration leads to increased glycosylation of proteins, particularly

lipoproteins. Glycosylation of low-density lipoprotein (LDL) has been shown to enhance its susceptibility to oxidation, which triggers the atherosclerotic processes. The Honolulu Heart Study, the Bedford Study, and the Pathological Determinants of Atherosclerosis in Youth Study are some of the studies that have demonstrated the association of hyperglycemia with CAD.[49–51] Reduction of CAD events with intensive glycemic control using insulin was shown in the randomized trial of insulin–glucose infusion followed by subcutaneous insulin treatment in diabetes patients with acute MI,[52] which indirectly proves the association of hyperglycemia with CAD. In the CUPS, prevalence of CAD was seen to increase with increase in fasting plasma glucose levels, even among nondiabetic subjects. The odds ratio (OR) for CAD increased with increase in quartiles of fasting plasma glucose and 2 h postglucose load plasma glucose, indicating a strong association of plasma glucose levels with CAD (**Figure 4**), which also means that in Indians, as shown in the West, the clock for CAD starts "ticking" even at the IGT stage itself. It also indicates that the plasma glucose–CAD relationship is a continuum and that there is no threshold value of risk.[53]

Sleep Apnea and Coronary Artery Disease

Sleep-related breathing disorders are highly prevalent in patients with established cardiovascular disease.[54] Obstructive sleep apnea (OSA) has been linked to increased cardiovascular morbidity and mortality from both coronary heart disease and stroke,[55,56] but whether this risk is due to coexistent known cardiovascular risk factors or specific effects of OSA remains to be established. Udwadia and coworkers[57] have shown that higher prevalence of OSA in urban middle-aged Indian men is striking and may have major public health implications in a developing country with limited health resources.

Blood Pressure and Coronary Artery Disease

The high risk for CAD among hypertensive subjects has been documented in several studies. Further, intervention studies using antihypertensive medications have shown significant decrease in CAD risk.[58,59] The overall prevalence of hypertension in the CUPS was 22.1%, of which 8.2% had "known" hypertension. Coronary artery disease was much more prevalent among hypertensives than normotensives. The CAD risk was even higher among subjects who both had diabetes and were hypertensive (OR 3.13, $p = .004$) (**Figure 5**). Both systolic and diastolic blood pressure showed a strong correlation with CAD on a univariate analysis in the CUPS study.[41]

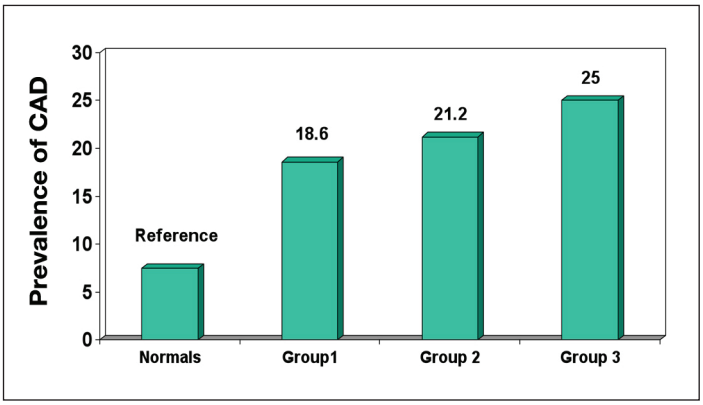

Figure 1. Prevalence of CAD among subjects with multiple risk factors.[41] Group 1, glucose intolerance (IGT + diabetes); group 2, glucose intolerance ([IGT + diabetes] + hypertension); group 3, glucose intolerance ([IGT + diabetes) + hypertension + dyslipidemia). Dyslipidemia = serum cholesterol ≥ 200 mg/dl or triglycerides ≥ 140 mg/dl.

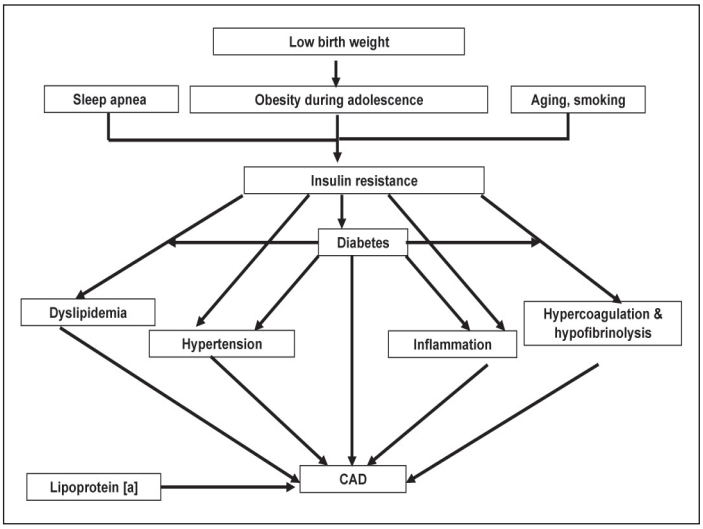

Figure 2. The interaction of cardiovascular risk factors.[46]

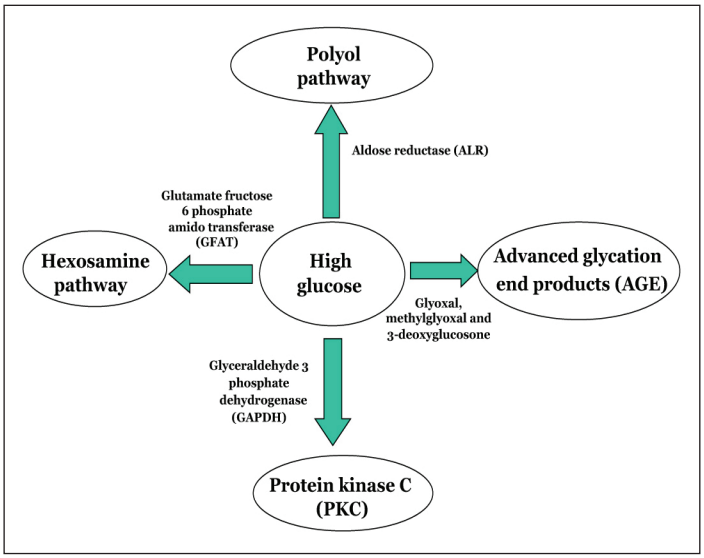

Figure 3. Multiple biochemical aberrations based on high glucose.

Dyslipidemia and Coronary Artery Disease

Dyslipidemias, which include high serum cholesterol, high serum triglycerides, high LDL cholesterol and low high-density lipoprotein (HDL) cholesterol, are known to be associated with diabetes. Several intervention studies have clearly shown reduction in CAD mortality through reduction of serum cholesterol and triglyceride levels.[60,61] However, the association of isolated hypertriglyceridemia with CAD is still a matter of debate.[61]

A LDL cholesterol level less than 100 mg/dl has been proposed as the treatment goal in diabetes patients by the recent NCEP guidelines.[62] A recent meta-analysis on the effect of statins on LDL cholesterol recommended using statins to lower LDL cholesterol markedly and suggested that the reduction of CAD risk was possible by almost 60%.[63] High-density lipoprotein cholesterol, in contrast to LDL cholesterol, is a protective lipoprotein with anti-atherogenic potential. It is also believed to reduce peroxidation, as it carries enzymes like paraoxanases.[64]

The prevalence of CAD in the CUPS increased with an increase in total cholesterol (trend χ^2 26.2, $p < .001$), low-density lipoprotein cholesterol (trend χ^2 24.5, $p < .001$), triglycerides (trend χ^2 9.96, $p = .002$), and total cholesterol/HDL ratio (trend χ^2 6.14, $p = .0132$). Age (OR 1.05, $p < .001$) and LDL cholesterol (OR 1.009, $p = .051$) were identified as the main risk factors for CAD by multiple logistic regression analysis.[41] In a large clinic-based study carried out on 17,855 type 2 diabetes subjects, the association of isolated hypertriglyceridemia and isolated hypercholesterolemia with CAD was assessed. The prevalence of CAD was significantly higher among patients with isolated hypercholesterolemia, isolated high LDL, and isolated low HDL cholesterol compared to normolipidemic individuals, but not in those with isolated hypertriglyceridemia.[65] Regression analysis revealed LDL cholesterol to be associated with CAD.[41]

It is important to note that, in CUPS, subjects with CAD had lipid levels that were much lower than the high-risk category described by NCEP guidelines.[9] For instance, the mean total cholesterol and LDL cholesterol in the nondiabetic groups with CAD were 182 ± 36 mg/dl and 118 ± 30 mg/dl, respectively. Indians are known to have much lower HDL cholesterol levels, and hence the total cholesterol/HDL cholesterol and LDL/HDL cholesterol rates are higher in Indians.[41] The OR for CAD was calculated in the CUPS in relation to total cholesterol/HDL ratio. A ratio of ≤ 4.0 was taken as the reference,

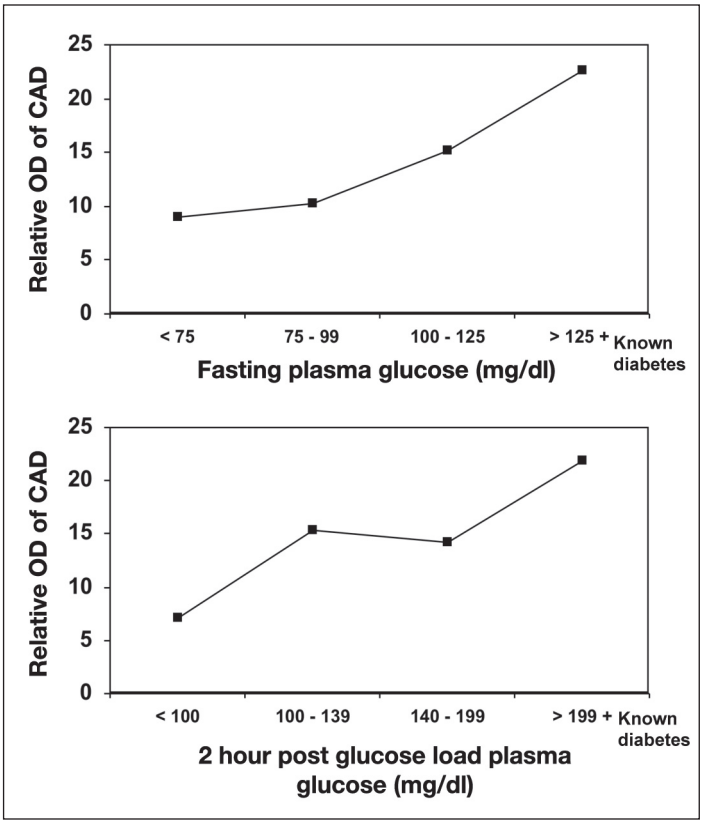

Figure 4. Odds ratio of CAD in relation to plasma glucose (CUPS).

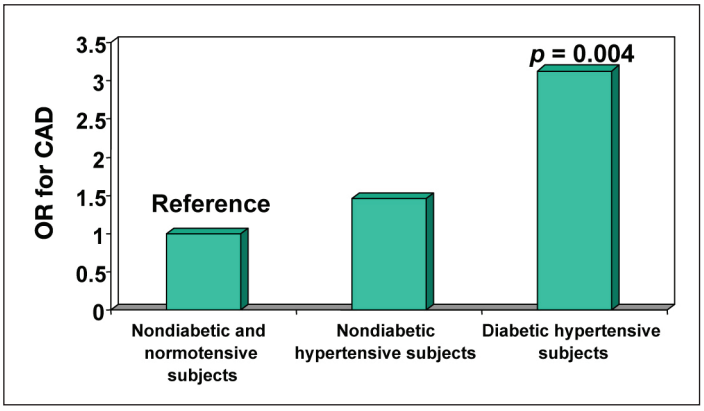

Figure 5. Odds ratio of CAD among subjects with diabetes and hypertension (CUPS).

and the OR for CAD for a total cholesterol/HDL ratio of 4.1–4.5 was 1.82, which increased further with further increase in this ratio. Recent studies have emphasized the role of small dense LDL in atherogenesis and have shown that diabetic subjects have higher levels of small dense LDL compared to nondiabetic subjects. A study in Birmingham, Alabama, revealed that migrant Indians have higher small dense LDL compared to their white counterparts.[66] The Chennai Urban Rural Epidemiology Study (CURES) conducted in South Indians showed that

small dense LDL levels were higher in diabetic patients and even higher in diabetic subjects with CAD, as shown in **Figure 6**.[67]

Clustering of Metabolic Risk Factors and Insulin Resistance Syndrome

Type 2 diabetes is a combination of several metabolic abnormalities, and most of these are preceded by insulin resistance. Fasting insulin levels have been found, in prospective studies, to be a surrogate marker of insulin resistance and a predictor of CAD.[68] Most of the cardiovascular risk factors like dyslipidemia, hypertension, obesity, central obesity, and glucose intolerance have been shown to be associated with insulin resistance, and a combination of these abnormalities could lead to CAD. The term "syndrome X" was first coined by Reaven[69] to denote this cluster, which is also called "metabolic syndrome" or "insulin resistance syndrome" (IRS). The metabolic cluster seems to explain a major part of the pathogenesis of CAD. In CUPS, the CAD risk increased with increase in the number of metabolic abnormalities. The same study also assessed the prevalence of IRS using the European Group of Insulin Resistance (EGIR) criteria and found that IRS was present in 11.2% of urban South Indians. It is to be noted, however, that this figure of 11.2% was based on the higher cutoff points that the EGIR recommends for dyslipidemia, i.e., serum triglyceride levels more than 200 mg/dl and/or serum cholesterol levels greater than 200 mg/dl. If the Adult Treatment Panel III guidelines, which have much lower cutoffs, had been used, the prevalence of IRS would have been obviously much higher. Clustering of these metabolic parameters was evident even among young individuals.[70] Misra and Vikram[71] described this clustering effect and suggested that body fat, dietary modification, physical inactivity, and stress are important contributory factors for high prevalence of metabolic syndrome in Indians, and the term "cardio-metabolic syndrome" is used for this entity.[72]

Asian Indians have higher prevalence of hyperinsulinemia, insulin resistance, and other components of metabolic syndrome. Obesity, particularly abdominal obesity, is considered to contribute to the increased insulin resistance in Indians. Though Indians have low rates of generalized obesity, the prevalence of abdominal obesity is higher compared to other ethnic groups.[73,74] Further, for any given degree of obesity, Indians also have higher body fat than other ethnic groups, and for any given body mass index, the waist-to-hip ratio was higher among Indians.[75] Finally, for any given body fat, Indians have higher insulin resistance compared to other ethnic groups.[73]

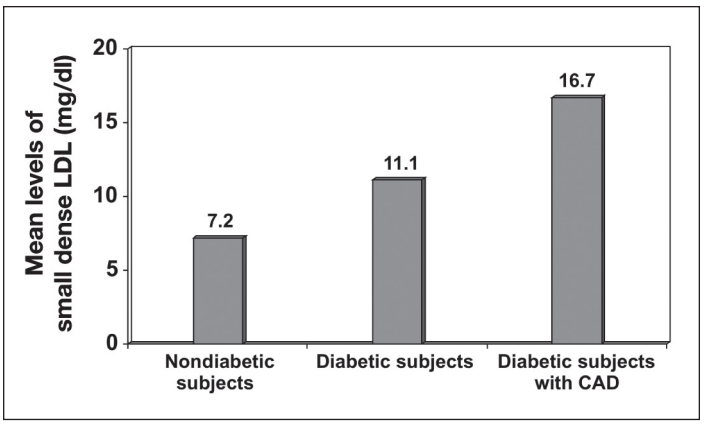

Figure 6. Mean levels of small dense LDL (CURES).[67]

Low Birth Weight

Low birth weight has been shown to contribute to insulin resistance among Indians.[76] It has been hypothesized that low birth weight followed by a tendency for obesity in childhood or adolescence could lead to IRS during adulthood (**Figure 2**). Indians have insulin resistance and adiposity even at birth when compared to Caucasians.[76] Barker and colleagues postulated that this was a result of fetal adaptation to inadequate intrauterine nutrition.[77] An alternative hypothesis is that CAD and low birth weight could share a common genetic predisposition. In India, according to the National Health Survey, the prevalence of low birth weight among neonates is 28%.[78] A strong association for low birth weight with insulin resistance has been shown in Indian children. A study of a cohort of 1492 subjects followed starting in 1969 revealed that the prevalence of diabetes was highest among subjects with lowest weight at age 2 and highest weight at age 12.[79]

Fibrinolytic Factors

Many of the new risk factors like plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and inflammatory markers like C-reactive protein (CRP) and interleukins have been included in the list of abnormalities under the insulin resistance syndrome.[80] Some of the comparative studies on migrant Indians have suggested that the excess risk for CAD seen among Indians could be partly explained by these risk factors.[81–83] Fibrinogen and PAI-1 levels have been found to be associated with angiographically proven CAD, and the relative ORs for CAD increased with increase in quartiles of fibrinogen and PAI-1.[82] A study from South India also showed a weak association of PAI-1 with CAD,[83] while another study on native Indians showed that PAI-1 correlated well with triglycerides.[84]

Lipoprotein (a)

Lipoprotein (a) [Lp(a)], an atherothrombogenic moiety, is a complex of apolipoprotein (a) [Apo(a)] and LDL, which is determined genetically.[85] It can competitively inhibit plasminogen activity, leading to impaired fibrinolysis. Lipoprotein (a) has also been implicated in enhanced oxidation and foam cell formation. The smaller the Apo(a), the higher are the Lp(a) levels and the risk for CAD. Lipoprotein (a) levels above 20 mg/dl are reported to be associated with a high risk of CAD.[86] In a South Indian study on 300 subjects, Lp(a) had an independent association with CAD in type 2 diabetes patients. An increase in Lp(a) was found to be associated with increase in carotid IMT, a preclinical atherosclerotic marker.[87] This suggests that Lp(a) is associated with CAD even at an early stage of atherosclerosis.

Homocysteine

Homocysteine, a sulfur-containing amino acid, is an atherothrombogenic moiety that triggers platelet adhesion in cell culture.[88] Homocysteine has been shown to be strongly associated with CAD in several studies.[89] Migrant Indian studies have shown higher levels of homocysteine compared to the native population.[90,91] However, studies on its association with CAD among native Indians have been consistently negative.[92,93] Yet these studies should be interpreted with caution, as they were based on small sample sizes, and moreover, oral methionine-loaded homocysteine levels were not assessed.

Inflammatory Markers

There is increasing evidence that inflammatory processes and specific immune mechanisms are involved in atherogenesis, and inflammatory markers are reported to be higher among subjects with insulin resistance and diabetes.[94] Inflammation is considered to be a part of insulin resistance syndrome,[95] and this, at least partly, explains the high risk for CAD among diabetic subjects. Inflammatory changes could take place near the rupture of the plaque, leading to instability in the fibrous tissue in the plaque. Studies on pro-inflammatory markers have revealed that cytokines like tumor necrosis factor α (TNF-α), CRP, and interleukin-6 are strongly associated with CAD. Studies suggest that TNF-α plays a key role in mediating insulin resistance as a result of obesity.[96] C-reactive protein levels seem to be higher in migrant Indians compared to other ethnic groups.[97,98] In a large study of 1025 subjects, CRP levels were 17% higher in Asian Indians compared with white Europeans. C-reactive protein also had a strong association with cardiovascular risk factors like obesity, insulin resistance, and lipids.[97] In another age-matched study on 82 Asian Indian men and 55 Caucasian men with similar body fat content and truncal skin-fold thickness, Asian Indians were shown to have elevated CRP levels, suggesting that pro-inflammatory factors may contribute to increased risk for diabetes and CAD.[98] Asian Indian children were also shown to have 104% higher levels of CRP compared to Europeans.[99] However, there have been very few studies on native Indians. One study showed that CRP correlated significantly with body fat.[100] In our study on 150 subjects, which included nondiabetic subjects without CAD and diabetic subjects with and without CAD, CRP levels were higher among diabetic subjects with and without CAD compared to nondiabetic subjects without CAD.[100] A review on the relevance of CRP in young individuals associates high CRP in Indians with excess body fat, subcutaneous fat, and physical inactivity.[101]

Other markers of CAD are endothelin 1, adhesion molecules like vascular cell adhesion molecule, intercellular adhesion molecule 1, E-selectin, and P-selectin, elevated levels of which have been shown to be associated with serious coronary events and angiographically documented CAD[102–105] in Western populations. Inhibiting the action of adhesion molecules has been a focus to prevent atherosclerosis.[106] Owing to ethnic differences in the prevalence of CAD, ethnic-specific studies on the association of these parameters with CAD are required.

Prevention of Coronary Artery Disease

India is now facing a double epidemic of diabetes and CAD. Research studies indicate that diabetes plays a contributory role for CAD in Indians by increasing the risk for hypertension, hypercholesterolemia, hypertriglyceridemia, low HDL cholesterol, and increasing PAI-1 and fibrinogen levels. Prospective longitudinal cohort studies for evaluation of coronary risk factors in India are the need of the day, as most of the current data are cross sectional in nature.

Pharmacological Intervention

Despite the fact that many of the risk factors for CAD are genetically inherited, pharmacological intervention has been found by prospective studies to reduce the incidence of CAD. Statin trials have demonstrated that reducing LDL cholesterol could be very beneficial in reducing cardiovascular mortality.[60,107,108] Trials using

fibrates have shown that reduced triglycerides and moderate elevation of HDL can prevent cardiovascular events.[109,110] The United Kingdom Prospective Diabetes Study (UKPDS) and Microalbuminuria, Cardiovascular, and Renal Outcomes in the Heart Outcomes Prevention Evaluation have shown that intensive hypertension control is beneficial in reducing cardiovascular events, even among diabetic subjects. However, in the UKPDS, good control of blood glucose by itself was not sufficient to significantly reduce risk of cardiovascular disease, although there was a 16% reduction. A multifactorial approach by good control of blood glucose, blood pressure, and serum lipids appears to be necessary to prevent CAD in diabetes patients.[111,112]

Lifestyle Changes

Dietary modification, regular physical activity, weight reduction, and cessation of smoking have been proven to be beneficial in preventing CAD. The Harvard Alumni Study documented that physical inactivity plays a role in CAD.[113] The CUPS revealed that subjects who performed light-grade activity had increased prevalence of not only CAD but also all cardiovascular risk factors compared to subjects who performed heavy-grade activity (**Figure 7**).[114] Though there are very few studies on the role of exercise in prevention of CAD in diabetes patients, there is ample evidence to support that exercise does reduce cardiovascular risk factors and thus can potentially be of great help in reducing CAD itself.[115–118]

In summary, given the explosion of diabetes and CAD in India, increased emphasis on lifestyle modification, including diet, exercise, weight reduction, and, whenever relevant, stress reduction, is urgently needed.

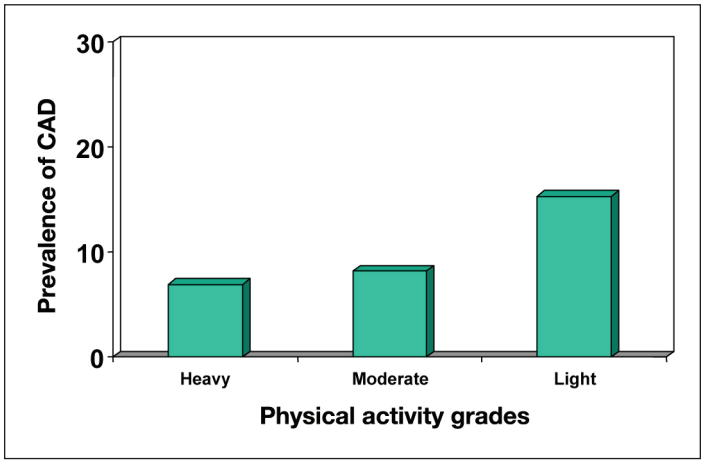

Figure 7. Prevalence of CAD in relation to grades of physical activity (CUPS).[114]

A comprehensive surveillance system of risk factors and CAD will be an invaluable public health research tool for monitoring population health status, guiding resource allocation and policy, identifying and prioritizing interventions for subpopulations at particular risk, identifying disparities in outcomes, and planning and evaluating health programs. Carefully planned prevention programs with intervention strategies could also be taken up in different parts of the country to prevent the double epidemic of diabetes and CAD, as both have common causative factors, and prevention strategies could also be combined judiciously to prevent both disorders, as this would make it more cost-effective.

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