REVIEW ARTICLE

Coronary Artery Disease and Diabetes - Indian Scenario

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ABSTRACT

Coronary artery disease (CAD) and diabetes have emerged as the major causes of mortality worldwide as the toll of infectious diseases have begun to wane. Escalation in prevalence of both these conditions appears to be more pronounced in developing countries, particularly in India. Ample evidence has accumulated for the high prevalence rates of diabetes and CAD among Indians. Both these diseases could rise from a common soil. It has been shown that the risk for CAD among diabetic subjects is greater by a factor of 2 to 4 compared to non-diabetic subjects. The 'Asian Indian paradox' is that high rates of CAD are seen despite low rates of conventional risk factors like obesity, smoking and hypertension. Therefore there is a great need for studying risk factors for CAD among Indians.

The prevalence of CAD in the Chennai Urban Population Study (CUPS), a population based study is 11% which is 10 times higher than that reported 40 years ago. Diabetic subjects in this study had a two fold higher risk for CAD compared to the subjects with normal glucose tolerance. The reason for the enhanced susceptibility for CAD among diabetic subjects is still not clear. As diabetes is a part of the insulin resistance cluster, which is a combination of hyperglycemia, central body obesity, dyslipidemia, and hypertension, there could be an interplay of these factors in enhancing the chances of developing CAD. In addition, low-grade inflammation due to insulin resistance contributes to plaque formation and rupture. This review discusses the role of a variety of cardiovascular risk factors in contributing to the excess CAD in diabetic patients with particular reference to the Indian subcontinent.

Key words : Coronary artery disease, Type 2 diabetes, Insulin resistance syndrome, CRP, Asian Indians, CUPS.

INTRODUCTION

Diabetes is increasing in alarming proportions worldwide[1]. As diabetes shares many characteristics and risk factors with CAD [2,3] the risk for CAD is also indirectly escalating with the increase in prevalence of diabetes. The risk factors that are common for both these disorders include age, hypertension, dyslipidemia, obesity and life style related factors like physical inactivity and stress. Several epidemiological studies have consistently shown that diabetes increases the risk for CAD by 2—4 times[2]. Moreover, CAD also occurs 2- 3 decades earlier among diabetic subjects [2,3]. Diabetes reduces the life expectancy by nearly eight years and increases the mortality markedly [4]. More than 80% of all deaths and 75% of all hospitalizations in diabetic patients are due to CAD[5,6]. Plaques have also been shown to be more vulnerable in diabetic subjects [7].

Though wide ethnic and geographical variations in the prevalence of both diabetes and CAD have been reported, the association between these two disease entities still remains strong. Diabetes abolishes the protective female gender effect and infact women with diabetes have an increased risk for CAD compared to men with diabetes [8]. The Organization to Assess Strategies for Ischaemic Syndromes (OASIS) study showed that diabetic subjects without prior CAD had a similar risk for developing CAD, as did non-diabetic subjects with prior CAD (5). Furthermore, the prognosis after a clinical event is worse in diabetic subjects compared to non-diabetic subjects. Indeed, the current NCEP guidelines have categorized diabetes as a cardiovascular risk equivalent [9]. A recent review on diabetes and atherosclerosis showed that the metabolic abnormalities due to diabetes predispose to vascular changes, which in turn lead to atherosclerotic end points[10]. Independent of the cardiovascular risk factors seen among non-diabetic subjects, diabetes specific factors also contribute to the increased CAD risk.

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HEALTH BURDEN DUE TO CAD AND DIABETES WORLDWIDE

CAD is ranked as the leading cause for death worldwide in 1990 and will continue to hold this position until 2020 [11]. 30.9% of all deaths in 1998 and 10.3% of disability adjusted life year loss [DALY's] was due to cardiovascular diseases[11]. In most of

the developing countries, the prevalence of CAD has increased dramatically while the reverse trend is seen in developed nations[12]. The contribution of developing nations to the cardiovascular burden is expected to be about 85% by 2020. Furthermore, the increase in CAD mortality in the developing countries from 1990 to 2020 is projected to be 120% in women and 137% in men [13,14]. These projections are based on conservative figures and changes in demography of the population. However, if increases in all the cardiovascular risk factors are taken into account, the escalation in CAD deaths would be quite alarming.

Diabetes is the fifteenth cause of death worldwide[11]. Recent statistics from the World Health Organization [WHO] show that in the year 1995, 135 million people had diabetes globally and these numbers are expected to increase to 300 million by the year 2025[1]. The increase projected for developing countries is a staggering 170% as against 42% for developed nations. Indeed, it is estimated that by the year 2025, developing countries would contribute over 75% of the diabetic subjects worldwide. The countries with the largest number of people with diabetes are India, China, and the U.S and these countries would continue to top the list even by the year 2025[1].

This article will focus on the twin burden due to diabetes and CAD in India as we are currently facing an epidemic of both conditions and will review Indian literature specifically looking at data from the Chennai Urban Population Study (CUPS).

EPIDEMIOLOGY OF CORONARY ARTERY DISEASE IN INDIANS

Estimates from the Global Burden of Disease Study project India will have the greatest burden due to coronary artery disease [11]. Over 9 million deaths in 1990 in the developing countries were due to CAD, of which, India alone contributed 2.4 million deaths (25%) [11,14]. In 1990, the prevalence of acute myocardial infarction mortality rates in India were 141 per 100, 000 in males and 136 per 100, 000 in females [14]. This is much higher than that reported 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]. According to the World Bank figures, the overall cardiovascular mortality in Indians is projected to rise by 103% in men and 90% in women between 1985 and 2015 [14]. It is even more disheartening to note that 52% of the CAD deaths in India occurred below the age of 70 years as compared to 22% in developed countries[14,15].

The predilection to CAD among Asian Indians was demonstrated nearly forty-five years ago by Shaper and Jones[16] in Uganda. Later studies from various parts of the world confirmed that migrant Indians have much higher prevalence of CAD as well as CAD mortality rates compared to the host populations of these countries[17-26]. Moreover Asian Indians develop CAD a decade earlier and have 2 to 4 times higher prevalence of CAD at younger ages ie premature coronary artery disease compared to Europeans [23,24]. The SHARE study demonstrated that South Asians had higher prevalence of cardiovascular disease compared to Europeans and Chinese living in Canada [25].

There is now accumulating evidence that the prevalence of CAD is rapidly raising within the Indian subcontinent also, particularly in urban areas. Chadha et al [27] reported the prevalence of CAD to be 9.7% based on a study in Delhi. The Jaipur Heart Watch showed that the prevalence of both CAD and cardiovascular risk factors is remarkably high[28]. A Meta analysis of the prevalence of CAD based on the surveys conducted in last 2 decades suggested that there was a nine-fold increase in CAD in urban populations and a two-fold increase in rural population [29]. Thus a dramatic increase in the prevalence of CAD has been projected in India in the next 15 years [14], which also adds to the health burden due to CAD among Indians [15].

EPIDEMIOLOGY OF DIABETES IN INDIANS

Of the 135 million people worldwide, affected by diabetes, India leads the world with over 30 million people. Indeed nowhere is the diabetes epidemic more pronounced than in India as more than 57 million people are projected to have diabetes by the year 2025 [1]. Revised statistics put the figure at 80.9 million diabetic subjects by the year 2030 [30]. Several lines of evidence for this rising prevalence of diabetes come from the recent studies in native Indians[31-35]. In 1970's, the prevalence of diabetes among urban Indians was reported to be 2.1% [36], in 1980's it was 8.2% [37] and this has now risen to 12.0% [31,38]. Studies on migrant Indians have indicated a two to three times higher risk for diabetes among Asian Indians compared to the indigenous population [39]. Furthermore, Indians tend to develop diabetes atleast a decade earlier compared to Europeans. Several native studies have shown that diabetic subjects have an increased tendency to develop macrovascular disease like coronary artery disease and peripheral vascular disease.[40-43]

THE CHENNAI URBAN POPULATION STUDY (CUPS)

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 [44]. 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). The prevalence of diabetes in this study population was 12%, and an additional 5.9% of subjects had impaired glucose tolerance [32]. CAD was diagnosed using medical history and Minnesota coding of 12 lead ECGs[40,45]. The overall prevalence of CAD was 11% in the total population. 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. This figure of 11% represents a ten-fold increase in prevalence of CAD in urban India during the last 40 years[40,46] and the figures are now approaching those reported in migrant Indians.[23,24,47]

In CUPS, the prevalence of CAD was higher among diabetic subjects [21.4%] (known diabetes 25.3% and newly diagnosed diabetes – 13.1%) compared to 14.9% among subjects with

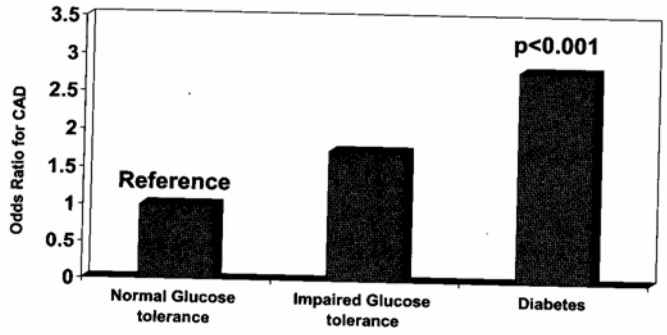

Figure 1 : Risk for CAD among subjects with glucose intolerance (CUPS)[40]

impaired glucose tolerance (IGT) and 9.1% among subjects with normal glucose tolerance[40]. Prevalence of known myocardial infarction was three times higher in subjects with diabetes compared those without. The odds ratios for CAD in different stages of glucose intolerance is presented in Figure 1. The risk for CAD thus seems to increase even at the stage of impaired glucose tolerance.

PRE-CLINICAL ATHEROSCLEROTIC MARKERS IN DIABETIC AND NON-DIABETIC SUBJECTS – IN THE CUPS STUDY

To further confirm the high risk for CAD among diabetic subjects, the pre-clinical atherosclerotic markers (structural and functional) were assessed in diabetic and non-diabetic subjects from the CUPS population. Structural changes in the arteries were assessed by studying the carotid Intimal Medial Thickness (IMT)[48] while functional changes were assessed by studying endothelial dysfunction by flow mediated dilatation and arterial stiffness studies[49,50].

The mean IMT values among diabetic subjects were significantly higher (0.95 ± 0.31mm) compared to normal subjects (0.74 ± 0.14mm) ($p<0.001$)[51]. The range of IMT values in non-diabetic subjects was 0.5 – 1.2 mm and in diabetic subjects, 0.4 – 3.0 mm. An IMT value $\geq$ 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 non-diabetic subjects.[51]

Endothelial dysfunction was measured as flow mediated dilatation (FMD) of the brachial artery using high-resolution B mode ultrasonography. FMD was found to be reduced in diabetic patients compared to age and sex matched non-diabetic subjects[52]. Arterial stiffness was assessed by measuring the Augmentation Index (AI) using the Sphygmocor machine. This was also found to be significantly greater among diabetic subjects compared to age and sex matched non-diabetic subjects [52]. Pearson correlation analysis of AI and FMD was done with the risk factors for CAD which revealed age, fasting plasma glucose and glycated haemoglobin to be positively associated with AI and negatively associated with FMD. These studies confirm that diabetic subjects have an increased tendency to develop premature atherosclerosis.

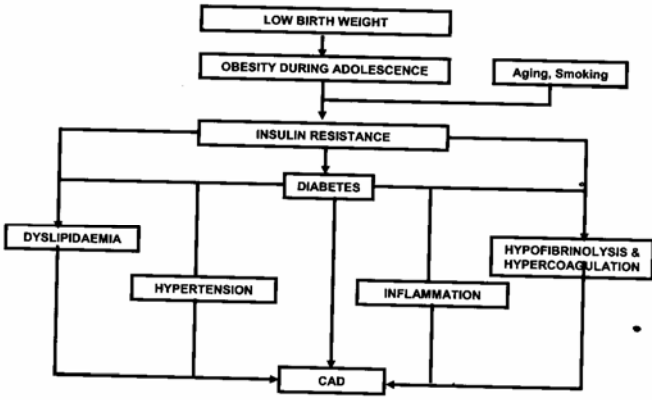

Figure 2 : The interlink of cardiovascular risk factors

WHY ARE DIABETIC SUBJECTS MORE PRONE TO CAD?

Several risk factors have been identified for CAD, which includes aging, smoking, strong family history of CAD and diabetes. Diabetes is a part of the insulin resistance cluster, which is a combination of hyperglycemia, central body obesity, dyslipidemia, and hypertension. Each of these components can independently contribute to the risk of CAD or may cluster to increase the risk of CAD [Figure 2]. Some of the risk factors for CAD with particular reference to studies in Indians are discussed below.

PLASMA GLUCOSE LEVELS AND CAD

Increased plasma glucose concentration leads to an increase in glycosylation of proteins, particularly lipoproteins. Glycosylation of LDL has been shown to enhance its susceptibility to oxidation, which triggers the atherosclerotic processes. Various studies in the west have demonstrated the association of hyperglycaemia with CAD, which includes the Honolulu Heart Study, Bedford study and the Pathological Determinants of Atherosclerosis in Youth (PADY) study.[53-55] The DIGAMI study showed that intensive glycaemic control using insulin administration reduced CAD events, which is an indirect proof for the association of hyperglycaemia with CAD[56]. 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. Prevalence of CAD increased with increase in fasting plasma glucose and 2-hour post load plasma glucose [Figure 3]. This means that in Indians the clock for CAD starts ticking even at values considered to be below, what is currently defined as IGT. This also indicates that the relation of plasma glucose with CAD is a continuum and there is no threshold value of risk.[57]

BLOOD PRESSURE AND CAD

Several studies have documented the high risk for CAD among hypertensives. Further evidence for this association comes from intervention studies using anti-hypertensive drugs which

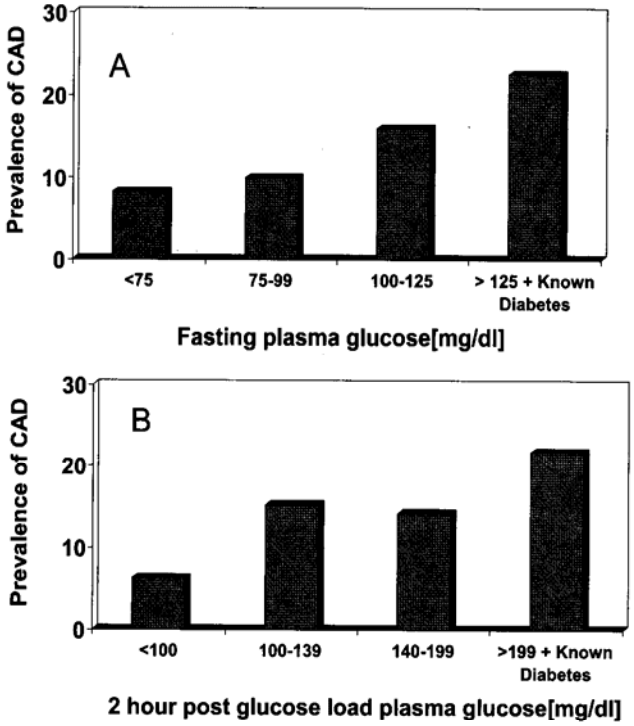

Figure 3 : Prevalence of CAD in relation to plasma glucose (CUPS)
A : Fasting plasma glucose
B : 2 hour post load plasma glucose

significantly decreases the risk for CAD [58,59]. The overall prevalence of hypertension in CUPS was 22.1% [60] of which 8.2% had known hypertension [61]. The prevalence of CAD was significantly higher among hypertensives compared to normotensives. The risk for CAD was even higher among subjects who were both diabetic and hypertensive [OR-3.13, p=0.004]. Both systolic and diastolic blood pressure showed a strong correlation with CAD on a univariate analysis in the CUPS study [40].

DYSLIPIDEMIA AND CAD

Diabetes is associated with lipid abnormalities, which includes high serum cholesterol, serum triglycerides, high low-density lipoprotein (LDL) cholesterol and low high-density lipoprotein (HDL) cholesterol. These abnormalities have also been implicated as risk factors for subjects with CAD. Evidence for this association arises from the several intervention studies which have clearly shown reduction in CAD mortality by reducing cholesterol and triglyceride levels[62-65]. However, the association of isolated hypertriglyceridemia with CAD is still a matter of debate[64].

The recent NCEP guidelines emphasize that LDL cholesterol less than 100 mg/dl should be the main treatment goal in diabetic patients [65]. A recent meta-analysis on effect of statins on LDL cholesterol suggested that use of statins to lower LDL cholesterol markedly and thereby reduce the risk of CAD by 60%[66]. In contrast to LDL cholesterol, HDL cholesterol is a protective lipoprotein with antiatherogenic potential. It is also believed to reduce peroxidation as it carries enzymes like paraoxanases [67].

In the CUPS study, the prevalence of CAD increased with increase in total cholesterol (trend chi square - 26.2, p<0.001) and 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). Risk factor analysis using multiple logistic regression analysis identified age (OR- 1.05, p<0.001) and LDL cholesterol (OR- 1.009, p=0.051) as the main risk factors for CAD (40). A large clinic based study carried out by us on 17,855 type 2 diabetic subjects assessed the association of isolated hypercholesterolemia and isolated hypertriglyceridemia with CAD [68]. 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. Regression analysis revealed LDL cholesterol to be associated with CAD[40]. Further, several intervention studies have clearly indicated the beneficial effect of lipid lowering therapy in decreasing the incidence of CAD[62,63].

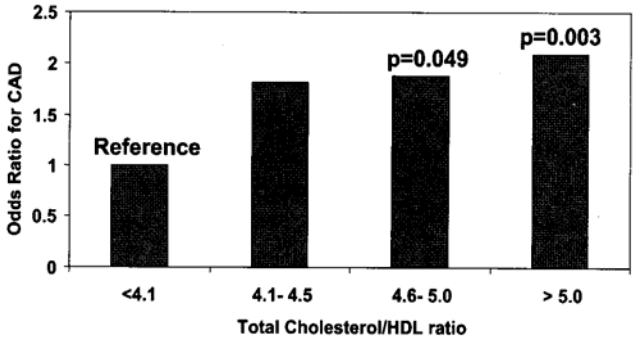

Figure 4 : Risk for CAD in relation to total cholesterol/HDL ratio (CUPS)[40]

It is noteworthy that in CUPS, subjects with CAD had lipid levels which were much lower than the high-risk category described by NCEP guidelines[9]. For example, the mean total cholesterol and LDL cholesterol in the non-diabetic 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[24]. The odds ratio for CAD was calculated in the CUPS study in relation to total cholesterol / HDL ratio. Ratio of ≤ 4.0 was taken as the reference, odds ratio for CAD for a total cholesterol / HDL ratio of 4.1 – 4.5 was 1.82 which increased further with further increase in ratio as shown in Figure 4. 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 non-diabetic subjects. A study in Birmingham, USA revealed that migrant Indians have higher small dense LDL compared to their white counterparts [69]. In a study in south Indians showed that small dense LDL levels were higher in diabetic patients and even higher in diabetics with CAD[70].

CLUSTERING OF METABOLIC RISK FACTORS AND INSULIN RESISTANCE SYNDROME

In Type 2 diabetes, there is combination of several metabolic abnormalities and most of these are preceded by insulin resistance. Prospective studies have shown fasting insulin levels to be

Table 1 : Prevalence of CAD among subjects with multiple risk factors (CUPS data)

Details	Prevalence of CAD
Normals (without hypertension and LDL < 100 mg/dL)	5.4%
Diabetes (without hypertension and LDL < 100 mg/dL)	11.1%
Diabetes + Hypertension	20.0%
Diabetes + Hypertension + LDL ≥ 100 mg/dL	21.1%
Diabetes + Hypertension + LDL ≥ 100 mg/dL + Central adiposity	28.9%

Hypertension : JNC VI guidelines
Central adiposity : Waist ≥ 90cm for males
Waist ≥ 80cm for females

a surrogate marker of insulin resistance and a predictor of CAD [71]. Insulin resistance has been shown to be associated with most of the cardiovascular risk factors viz., dyslipidemia, hypertension, obesity, central obesity and glucose intolerance, and a combination of these abnormalities could lead to CAD. Reaven first [72] coined the term "syndrome X" to denote this cluster which is otherwise called as 'metabolic syndrome' or 'insulin resistance syndrome [IRS]'. The metabolic cluster seems to explain a major part of the pathogenesis of CAD. In CUPS, it was noted that with increase in the number of metabolic abnormalities, the risk for CAD increased (Table 1). The same study also assessed the prevalence of Insulin Resistance Syndrome (IRS) study using the European Group of Insulin Resistance (EGIR) criteria [73] 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 higher cut off points that the EGIR recommends for dyslipidemia eg. serum cholesterol levels greater than 200 mg/dL and / or serum triglyceride levels greater than 200 mg/dL. If the ATP III guidelines [9], which have much lower cut offs are used, then the prevalence of IRS would be obviously much higher. Clustering of these metabolic parameters was evident even among young individuals [74]. This clustering effect was very elegantly described in a recent review by Misra [75], which suggests that body fat, dietary modification, physical inactivity and stress are important contributory factors for high prevalence of metabolic syndrome in Indians. In addition, clustering of risk factors of the insulin resistance syndrome has also been shown among native Indians [76-78]. Joshi [79] has recently coined the term cardio-metabolic syndrome for this entity and reviewed the Indian literature on this entity.

Hyperinsulinemia,[80] insulin resistance [81] and other components of metabolic syndrome have been shown to be more prevalent among Asian Indians. Obesity, particularly abdominal obesity, is considered to be contributor to the increased insulin resistance seen in Indians[82,83]. An interesting fact reported from migrant Indian studies is that even though Indians have low rates of generalized obesity, abdominal obesity is higher compared to other ethnic groups[84,85]. Furthermore, for any given degree of obesity, Indians also had higher body fat compared to other ethnic groups[84]. Again, for any given body mass index [BMI], the waist to hip ratio was higher among Indians [86]. Finally for any given body fat, Indians had higher insulin resistance compared to other ethnic groups [84].

Table 2 : Fibrinolytic Risk Factors and Coronary Artery Disease[84]

Results of univariate regression analysis using CAD as dependant variable

Variables	OR	95% CI	p Value
Plasminogen activator Inhibitor -1	1.032	1.008 – 1.056	**0.008**
Fibrinogen	1.007	1.006 – 1.016	**<0.0001**
Tissue plasminogen activator	1.124	1.009 – 1.253	**0.034**

LOW BIRTH WEIGHT

Recent studies have also shown low birth weight to be a contributor to insulin resistance among Indians [87]. It has been hypothesized that low birth weight followed by a tendency to obesity in childhood or adolescence could lead to IRS during adulthood. Studies on low birth weight and insulin resistance in Indian neonates have shown that Indians have insulin resistance and adiposity even at birth when compared to Caucasians [87].

Low birth weight has been associated with CAD and diabetes. Barker postulated that this was a result of fetal adaptation to inadequate intra-uterine nutrition[88]. It has been hypothesized that lower birth weight followed by increased obesity during adolescence could lead to insulin resistance syndrome during adulthood. An alternative hypothesis is that coronary heart disease and low birth weight share a common genetic predisposition. A longitudinal study by Eriksson et al [89] on 4630 Finnish men showed that subjects with low birth weight and low ponderal index have an increased risk of CAD.

In India, according to the National Health Survey, the prevalence of low birth weight among neonates is 28% [90]. A strong association for low birth weight with insulin resistance has been shown in Indian children [91]. A very recent study on 1492 subjects followed up from 1969 revealed that the prevalence of diabetes was highest among subjects with lowest weight at age 2 and highest weight at age 12.[92]

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 has been recently included in the list of abnormalities under the insulin resistance syndrome. 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 [93-95].

The fibrinolytic system plays an important role in homeostasis. It regulates the removal of thrombi from the vascular bed and maintains vascular potency. In the fibrinolytic cascade removal of fibrin clot is one of the main events and this is regulated by a balance between plasminogen activators and inhibitors which include tissue plasminogen activator [tPA] and plasminogen activator inhibitor [PAI-1]. Fibrinogen, a key element in the co-

agulation cascade has been shown to be associated with enhanced platelet aggregation and smooth muscle cell proliferation [93].

Recent studies from our centre have shown fibrinogen and PAI-1 levels to be associated with angiographically proven CAD [92] and the relative odds ratios for CAD increased with increase in quartiles of fibrinogen and plasminogen activator inhibitor [86]. Summary of the risk contributed by the fibrinolytic risk factors is presented in Table 2. 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 a study from South India [95], while another study on native Indians showed that PAI-1 correlated well with triglycerides.[96]

LIPOPROTEIN (a)

Lipoprotein(a) is a complex of Apolipoprotein (a) and LDL which is genetically determined.[97] Lipoprotein (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. 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.[98] Lipoprotein(a) levels above 20mg/dl are reported to be associated with a high risk for CAD.[99]

Earlier studies have yielded contradictory results for the association of Lp(a) with CAD. In a south Indian study on 300 subjects, Lp(a) had an independent association with CAD in Type 2 diabetic patients[100]. Several other studies have supported this association[101-103]. Very recently an increase in lipoprotein (a) was associated with increase in carotid intimal medial thickening, a preclinical atherosclerotic marker [104]. 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

Homocysteine, a sulphur containing amino acid is a atherothrombogenic moiety which triggers platelet adhesion in cell culture [105]. Homocyteine has been shown to be strongly associated with CAD in several studies [106]. Migrant Indian Studies have shown higher levels of homocysteine compared to native population [107,108]However studies on its association with CAD among native Indians have been consistently negative [109,110]. The results of native Indian studies should be interpreted with caution as all the studies are based on small sample size 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. Further, studies have revealed that inflammatory markers are higher among subjects with insulin resistance and diabetes [111]. Inflammation is considered to be a part of the insulin resistance syndrome [112] and this to some extent explains the high risk for CAD among diabetic subjects. Inflammatory changes could take place near the rupture of the plaque, leading to instability of the fibrous tissue in the plaque, thus facilitating the risk of chronic thrombosis. Studies on proinflammatory makers have revealed that cytokines like Tumour necrosis factor - α [TNF - α], C-reactive protein [CRP] and interleukin – 6 [IL – 6] are strongly associated with CAD. Recent studies suggest that TNF- α plays a key role in mediating insulin resistance as a result of obesity [113].

The inflammatory marker, CRP has received a lot of attention recently in the field of cardiology. Given the lipoprotein binding and complement activation of CRP and its localization in atherosclerotic vessels, there is a strong likelihood that CRP may be involved in the atherosclerotic process. CRP levels seem to be higher in migrant Indians compared to other ethnic groups [114,115]. This is considered to be one of the reasons for the high prevalence of heart disease among Indians [114]. In a large study on 1025 subjects, CRP levels were 17% higher in Asian Indians compared with European whites. CRP also had a strong association with cardiovascular risk factors, like obesity, insulin resistance and lipids. In another age matched study on 82 Asian Indian men and 55 Caucasian men with similar body fat content and truncal skinfolds thickness, Asian Indians had elevated CRP suggesting pro-inflammation which may contribute o increased risk for diabetes and CAD. A study on children also suggested that Asian Indian children had 104% higher CRP levels compared to Europeans [116]. However, there have been very few studies on native Indians with one study showing that CRP correlated significantly with body fat [117]. In our study on 150 subjects, which included non-diabetic subjects without CAD, diabetic subjects with and without CAD, CRP levels were higher among diabetic subjects with and without CAD compared to non-diabetic subjects without CAD [Mohan et al (under publication)]. A very recent review on the relevance of CRP in young individuals[118] associates high CRP in Indians with excess body fat, subcutaneous fat and physical inactivity.

PREVENTION OF CAD

India is now facing a double epidemic of CAD and diabetes. Based on our research studies and that of others, it appears that diabetes plays a contributory role for CAD in Indians by increasing the risk for hypertension, hypercholesterolaemia, hypertriglyceridaemia, low HDL-cholesterol and increased plasminogen activator inhibitor - 1 and fibrinogen levels. We urgently need prospective cohort studies for evaluation of coronary risk factors in India as most data are cross-sectional in nature. However based on the risk factors, what is the available evidence for prevention of CAD?

PHARMACOLOGICAL INTERVENTION

Though many of the risk factors are genetically inherited, many prospective studies have shown pharmacological interventions can reduce incidence of CAD. Statin trials have demonstrated that reducing LDL cholesterol to be very beneficial in reducing the cardiovascular mortality [62,63,119,120]. Trials using fibrates, have shown that reduced triglycerides and moderate elevation of HDL

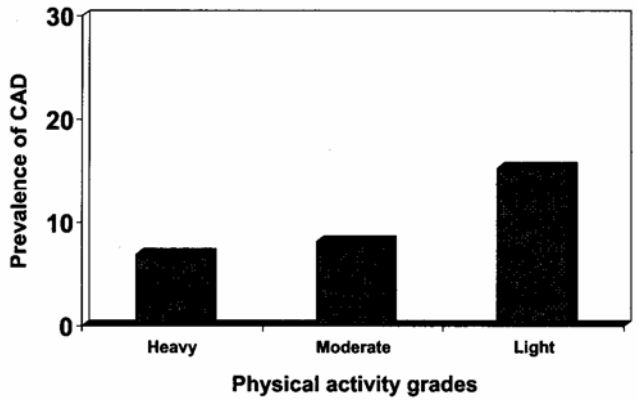

Figure 5 : Prevalence of CAD in relation to grades of physical activity (CUPS)

cholesterol can prevent cardiovascular events[121,122]. The UKPDS and MICRO-HOPE have shown intensive hypertension control to be beneficial in reducing cardiovascular events even among diabetic subjects[123,124]. However in the UKPDS good control of blood glucose alone was not sufficient to significantly reduce risk of CVD although there was a 16% reduction [125]. Probably a multifactorial approach by good control of blood glucose, blood pressure and serum lipids is necessary to prevent CAD in diabetic patients. Indeed, a recent Danish study demonstrated that a multifactorial approach of controlling lipids, blood pressure and hyperglycaemia significantly reduced CAD risk in diabetic patients.[126,127]

LIFE STYLE CHANGES

Dietary modification, regular physical activity, weight reduction and cessation of smoking have been shown to have beneficial effects in preventing CAD. The Harvard Alumni Study documented that physical inactivity plays a role in CAD [128]. Intra urban differences in the prevalence of the components of metabolic syndrome was observed which indicates the role of physical inactivity and dietary changes towards metabolic syndrome [32,73,129]. The CUPS study revealed that subjects who performed light grade activity had increased prevalence of not only CAD [Figure 5] but also all cardiovascular risk factors compared to subjects who performed heavy grade activity. Though there are very few studies on the role of exercise in prevention of CAD in diabetic patients, there is ample evidence to support that exercise does reduce cardiovascular risk factors including prevention of diabetes itself and thus can be of great help in reducing CAD.[130-132]

Given the explosion of diabetes and CAD in India, increased emphasis on life style modification including diet, exercise and stress reduction by yoga and other methods is the urgent need of the hour. Carefully planned prevention programs 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 common prevention methods.

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