18

R Deepa, K Gokulakrishnan, V Mohan

Coronary Artery Disease among Indian Diabetic Subjects

INTRODUCTION

Type 2 diabetes, one of the top five causes for mortality[1] presently affects more than 170 million individuals worldwide.[2] Diabetes is not only a mixture of several metabolic abnormalities; it also affects the vascular tree resulting in multiple micro- and macrovascular complications.[3] Premature cardiovascular morbidity and mortality is reported to be more common in diabetic subjects.[4] All these make diabetes an expensive disease. Over 8% of total health care expenditure in many countries is attributed to diabetes[5] and over 80% of deaths in diabetic subjects are due to cardiovascular disease, of which 2/3rd are due to coronary artery disease (CAD). It is estimated that in the year 2000, 2.9 million deaths were due to diabetes, which is nearly 5% of the total deaths reported worldwide.[1] The scenario is even worse in developing countries, particularly India.

EPIDEMIOLOGY OF DIABETES AND CAD—INDIAN SCENARIO

It is suggested that more than one-fifth of world's population (one billion people) lives in India and an additional 15 million Indians live outside India. Earlier studies on migrant Indians showed increased prevalence of diabetes among Indians compared to the indigenous population.[6,7] Over 35 million diabetic subjects reside in India making India, the diabetic capital of the world. These numbers are expected to increase by the year 2030.[2]

Indians also have three times higher risk of developing CAD compared to Chinese and are 20 times more likely to die due to CAD compared to native black or white South Africans.[8,9] The SHARE study demonstrated that south Asians had higher prevalence of cardiovascular disease compared to Europeans and Chinese living in Canada.[10] Moreover, Indians also tend to develop CAD two to three decades earlier compared to Europeans.[11] This predilection for CAD among Indians was reported fifty years ago,[12] which was confirmed later by several studies.[13,14] In India, approximately 2.78 million deaths are due to cardiovascular disease, of which over 50% is due to CAD, making CAD the number one killer disease in our country.[15] Prevalence of CAD in Indians

has been shown to be escalating in alarming proportions in the last few decades. The prevalence of heart disease in 1950s was 1.05%; this increased to 9.7% in 1990 and to 11.0% by 2000 in urban populations[16-19] (Figure 18.1). In the Jaipur Heart Watch-2 study conducted in 2002, prevalence of CAD was reported to be 8.2%.[20] This rising trend in CAD will shortly make India, the leader in CAD death rates also.[21] Thus India faces the dangerous dual epidemic of diabetes and CAD and in many respects, the aetiopathogenesis of both conditions may be similar.

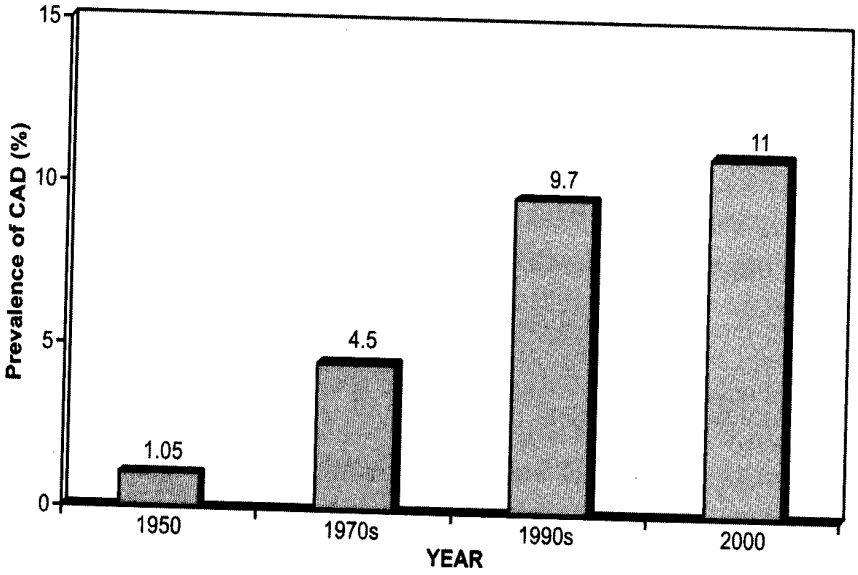


FIGURE 18.1: Rising prevalence of CAD in India[16-19]

CORONARY ARTERY DISEASE-DIABETES LINK

The risk for CAD among diabetic subjects is remarkably higher compared to non-diabetic subjects.[22,23] The risk for death due to CAD in diabetic subjects with one prior myocardial infarction (MI) is similar to that seen in a non-diabetic subjects with an earlier MI, while the risk is tripled in diabetic subjects with known MI.[24] The life expectancy of a diabetic patient is reduced by 30% compared to non-diabetic subjects which translates to 8 years loss of life years in diabetic subjects.[25] Further, the protective female gender effect in pre-menopausal women is abolished in diabetic females.[26]

THE CHENNAI URBAN POPULATION STUDY (CUPS) AND CHENNAI URBAN RURAL EPIDEMIOLOGY STUDY (CURES)

The Chennai Urban Population Study (CUPS) is a population-based study involving two residential areas representing the lower and middle income group in Chennai (formerly Madras) in south India. All individuals aged over 20 years living in these two colonies were requested to participate in the study. Of the total of 1,399 eligible subjects (age ≥ 20 years), 1,262 (90.2%) participated in the study. The study subjects underwent a glucose tolerance test (GTT) and were categorised

as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or diabetes. 12 lead ECG was also performed and CAD was diagnosed based on previous medical history of CAD and/or Minnesota coding of ECGs.[27]

The Chennai Urban Rural Epidemiology Study (CURES), an ongoing epidemiological study conducted on a representative population (aged ≥ 20 years) of Chennai (formerly Madras), the fourth largest city in India.[28] Briefly, in Phase 1 of the urban component of CURES, 26,001 individuals were recruited based on a systematic random sampling technique. Fasting capillary blood glucose was determined using a One Touch Basic glucose meter (Life scan, Johnson and Johnson, Milpitas, California, USA) in all subjects. Subjects were classified as 'known diabetic subjects' if they stated that they had diabetes and were on the treatment.

In Phase 2 of CURES, all the known diabetic subjects (n=1529) were invited to the centre for detailed studies on vascular complications. In Phase 3 one in tenth of the study subjects in Phase 1 were invited to the centre for detailed studies.[28]

Prevalence of diabetes: Prevalence of diabetes in CUPS study was 12.0%.[27] In CURES the prevalence of diabetes is 15.5%. The present prevalence is 70% higher compared to that reported in the 1980s.[29] This discussed in more detail in Chapter "Prevention of Diabetes."

Prevalence of CAD: In CUPS , overall, 11% of the total population had CAD and the age-standardised prevalence (standardised to the 1991 census of Chennai) was 9.0%.[30] 1.2% had documented myocardial infarction, 1.3% had Q wave changes, 1.5% had ST segment and 7.0% T wave abnormalities. The overall figure of 11% of CAD in the population represents a ten-fold increase in prevalence of CAD in urban India during the last 40 years (Figure 18.2).[19]

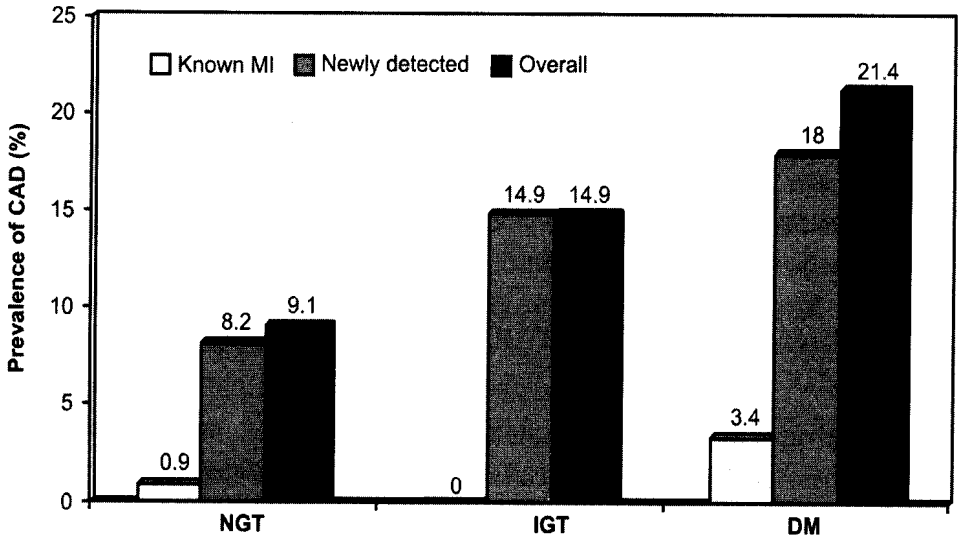


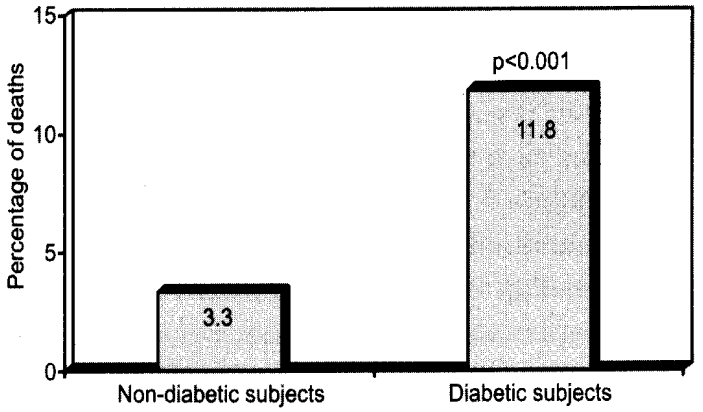
Figure 18.2: Prevalence of CAD in subjects with and without diabetes. The Chennai Urban Population Study [CUPS][19]. Newly detected CAD was diagnosed based on electrocardiographic changes suggestive of ST segment depression, Q wave changes and/or T wave inversion using appropriate Minnesota codes

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 impaired glucose tolerance (IGT) and 9.1% among subjects with normal glucose tolerance.[19] Prevalence of known myocardial infarction was three times higher in subjects with diabetes compared those without. At every age point, subjects with diabetes and impaired glucose tolerance had higher prevalence of CAD compared subjects with normal glucose tolerance. The risk for CAD thus seems to increase even at the stage of impaired glucose tolerance.

MORTALITY DUE TO CAD IN DIABETIC SUBJECTS

Mortality among diabetic subjects with CAD is higher than in non-diabetic subjects.[22] Studies have also shown that the myocardial infarction in diabetic subjects is more extensive and reccurrence is more common in them compared to non-diabetic subjects. Furthermore, the prognosis after a clinical event is worse in diabetic subjects compared to non-diabetic subjects.[24] A 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.[30] Very high risk for CAD among diabetic subjects lead the American Associations to label diabetes as a cardiovascular risk equivalent.[31]

In the CUPS study, there were 50 deaths out of the 1,140 subjects during the median follow up period of six-years.[32] The overall crude all cause mortality rate was 7.0 per 1,000 person years, age standardised mortality rate was 5.1 per 1,000 person years. The percentage of deaths was significantly higher among diabetic subjects (17/143, 11.9%) compared to non-diabetic subjects [33/997, 3.3%, p <0.001 (Figure 18.3)]. This translates to an all cause mortality of 18.9 per 1,000 person years (age standardised: 6.3 per 1000 person years) among the diabetic subjects compared



MORTALITY RATE:
Diabetic subjects: 18.9 per 1,000 persons years
Non-diabetic subjects: 5.3 per 1,000 persons years

FIGURE 18.3: Mortality in diabetic and non-diabetic subjects
The Chennai Urban Population Study [CUPS][32]

to an all cause mortality of 5.1 per 1,000 person years (age standardised: 4.4 per 1,000 person years) among non-diabetic subjects.

Mortality due to cardiovascular (52.9% vs 24.2%, p=0.042) and renal causes (23.5% vs 6.1%, p=0.072) were higher among diabetic, compared to non-diabetic subjects. The hazards ratio for diabetes for mortality due to cardiac vascular disease was 7.8 (95% CI: 3.0 – 20.2, p<0.001). Another interesting observation is that out of the total of 1,070 subjects, who had baseline information on coronary artery disease, recurrence of coronary artery disease was observed in 4.2%, and all these occurred in diabetic subjects.[32]

PATHOGENESIS OF ATHEROSCLEROSIS IN DIABETIC SUBJECTS

Among diabetic subjects prevalence of several cardiovascular risk factors is higher resulting in increased risk for atherosclerosis. Endothelial cells, smooth muscle cells and extracellular matrix like elastic elements, collagen and proteoglycans are the basic constituents of the walls of blood vessels. The vessel wall has three layers, the innermost layer, the tunica intima, consists of the endothelium, a small amount of underlying connective tissue and an internal elastic lamina, which separates it from the media. The endothelium contributes to the haemostatic barrier and provides the vasoreactive properties of the blood vessel. The middle layer, the tunica media is made up mostly of smooth muscle cells and is the thickest layer in the arteries. The outer layer, the tunica adventitia, consists of collagen, elastin, and other extracellular matrix proteins interspersed with fibroblasts. The composition and thickness of the adventitia determines the compliance of the blood vessel. Though this configuration remains same for all the arteries, the relative amount of the basic constituents could vary depending on the local requirements.

This process involves the macrophage that develops into a foam cell and gets deposited within the junction of the tunica intima and tunica medial layers of the artery during the first weeks of life and later progresses into a fibrous atheroma after several years.[33] Further, all the risk factors operating in non-diabetic subjects operate in diabetic subjects, but at a higher degree. Extensive studies in the last four decades have improved the knowledge of both causative factors and pathophysiology in diabetic subjects.[34]

The earlier stages of atherosclerosis involves both functional and structural changes in the arteries. These changes can be studied using sophisticated non-invasive techniques like high resolution ultrasound. These pre-clinical atherosclerotic markers have gained wide recognition in the field of cardiology as they are useful surrogate markers for CAD and can also be used in studies on prevention of CAD.

In the CUPS study we examined the carotid intimal medial thickness (IMT) in diabetic and non-diabetic subjects. The mean IMT values among diabetic subjects were higher (0.95 ± 0.31 mm) compared to control subjects (0.74 ± 0.14 mm).[35] 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. A study from western India has shown that IMT correlates with microalbuminuria in subjects with and without CAD.[36] A study from northern India has shown IMT to be associated with post-prandial hypertriglyceridaemia.[37] In the CURES study we showed that subjects with glucose intolerance had significantly higher mean IMT values compared to subjects with normal glucose tolerance (NGT: 0.69±0.12 mm, IGT: 0.75±0.16 mm, NDD: 0.79±0.19 mm, and KD: 0.87±0.24 mm), $p<0.001$. This indicates that IMT increases progressively with increasing severity of glucose intolerance.[38]

We also demonstrated that atherosclerosis manifests earlier among diabetic subjects. 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%), $p < 0.0001$.[40] Similarly arterial stiffness was measured by the augumentation index of the radial artery by the Sphygmocor. Arterial stiffness was found to be significantly greater in diabetic subjects (augumentation index- 27.48 ± 7.41%) compared to age and sex matched non-diabetic subjects (19.10 ± 8.19%), $p < 0.0001$.[39]

RISK FACTORS FOR CAD

Several risk factors have been identified for CAD in the general population, which includes aging, smoking, strong family history of CAD and diabetes. The INTERHEART study involving 15,152 cases and 14,820 controls from 52 countries revealed nine risk factors for CAD, which includes abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors decreased, consumption of fruits and vegetables, excess alcohol intake and physical inactivity.[40] Usual metabolic abnormalities like hyperglycaemia, hypertension and hyperlipidaemia complicate atherosclerosis in diabetes. Additionally newer risk factors are also involved in this phenomenon and some of them discussed below:

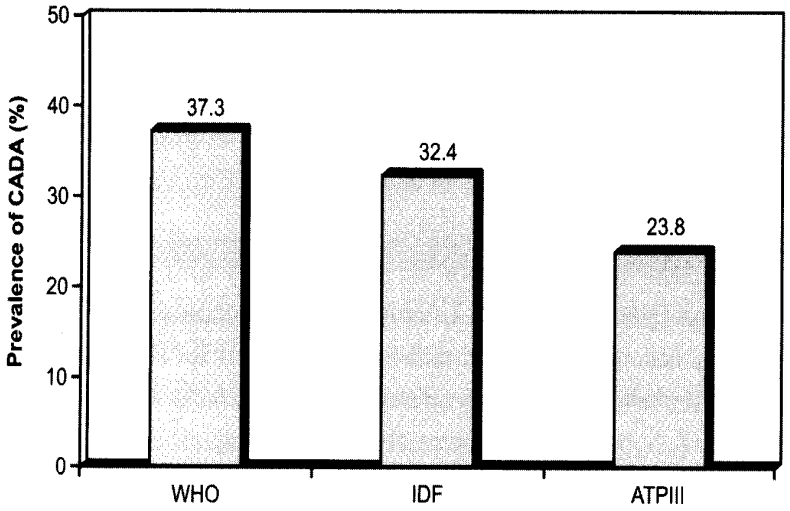
METABOLIC CLUSTER AND CAD

Several epidemiological studies have shown that metabolic cluster contributes to CAD. Insulin resistance plays a central role in metabolic abnormalities as it clusters with hyperinsulinaemia, hypertension (HTN), glucose intolerance, increased triglyceride, decreased HDL cholesterol levels, central and overall obesity. This was first identified by Reaven and termed as 'Syndrome X' which was later renamed as the metabolic syndrome or the insulin resistance syndrome (IRS).[41] This syndrome has been recognised as a major risk factor for coronary artery disease (CAD).[42,43]

Studies by Laasko et al[44] and Meigs et al[45] have shown using factor analysis that the metabolic abnormalities cluster and result in CAD. In the CUPS study using factor analysis, we showed that the components of metabolic syndrome—insulin resistance (HOMA IR), obesity, hyperglycaemia and hypertriglyceridaemia clustered in native Indian population and this cluster is associated with

hypertension.[46] An earlier study conducted on 654 non-diabetic subjects aged ≥ 40 years also showed similar results. The insulin resistance factor was found to cluster with hypertension through obesity indices.[47] In CUPS, CAD also showed a strong association with components of metabolic abnormalities which includes hyperglycaemia, hypertension and dyslipidaemia.[48, 49]

In CURES, we looked at the association of CAD with metabolic syndrome defined by three different criteria, the World Health Organisation (WHO), Adult Treatment Panel (ATPIII) and International Diabetes Federation (IDF) criteria.[50] Prevalence of CAD was higher among subjects with metabolic syndrome irrespective of whichever definition was used. However, metabolic syndrome defined using WHO criteria had highest odds ratio for CAD compared to other definitions (Figure 18.4). This could probably be due to inclusion of insulin resistance in the WHO criteria of metabolic syndrome.



CAD was diagnosed based on a past history of documented myocardial infarction and /or medical therapy (aspirin or nitrates) or revascularisation for CAD and/or electrocardiographic (ECG) changes suggestive of Q wave changes using appropriate Minnesota codes

FIGURE 18.4: Prevalence of CAD among subjects with metabolic syndrome[50]

INFLAMMATORY MARKERS

Several studies have shown an association between inflammatory markers with diabetes. Chronic low grade inflammation is considered to play a contributory role in both diabetes and CAD. Inflammation has been documented to be increased even during the insulin resistance stage which continues during the diabetes stage and eventually results in CAD. Inflammatory changes could also 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 markers 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 CRP plays a key role in mediating insulin resistance and coronary artery disease.[51,52]

Studies conducted in UK has shown that CRP levels are higher in migrant Indians compared to other ethnic groups.[53,54] This is suggested as one of the reasons for the high prevalence of heart disease among Indians. CRP also has a strong association with cardiovascular risk factors, like obesity, insulin resistance and lipids. A study on children also suggested that Asian Indian children had higher CRP levels compared to Europeans.[55] However, there have been very few studies on native Indians with one study showing that CRP correlated significantly with body fat.[56] 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 coronary artery disease.[57] CRP showed a strong association with CAD, even after adjusting for age and gender, and the association was abolished when body fat was added into the model (Figure 18.5). A recent review on the relevance of CRP in young individuals associates high CRP in Indians with excess body fat, subcutaneous fat and physical inactivity.[58]

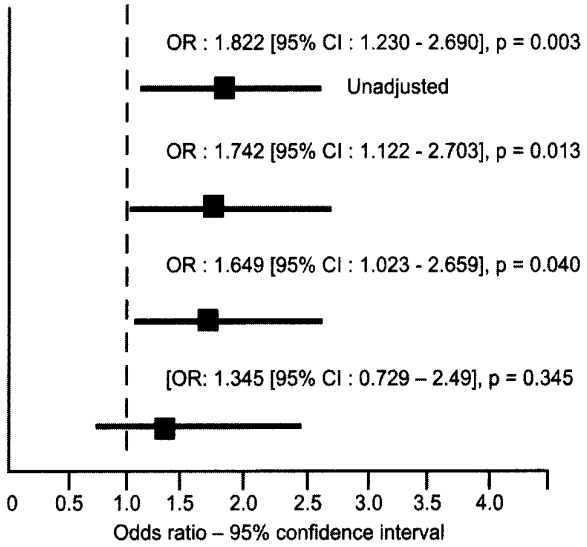


FIGURE 18.5: Regression analysis using CAD as dependent variable.[57] The odds ratio and 95% confidence interval of log transformed hs-CRP is presented here

FIBRINOLYTIC MARKERS

Insulin resistance not only clusters with classic cardiovascular risk factors like hypertension and dyslipidaemia, but also with several disorders of coagulation and fibrinolysis. Patients with insulin resistance syndrome and diabetes mellitus tend to have increased plasminogen activator inhibitor (PAI-1) levels. The later have been shown to be associated with a number of atherosclerotic risk

factors. Decreased fibrinolysis, increased PAI-1 levels, increased t-PA and increased fibrinogen levels are now considered to be part of the metabolic syndrome.[59] Proinsulin and insulin induce production of PAI-1 in experimental models.[60] Our studies on diabetic and non-diabetic subjects with CAD have shown fibrinogen and PAI-1 levels to be associated with angiographically proven CAD[61] and the relative odds ratios for CAD also increased with increase in quartiles of fibrinogen and plasminogen activator inhibitor.[61]

OTHER ATHEROGENIC MARKERS

Small Dense LDL

In diabetic subjects, LDL tend to get modified due to hyperglycaemia and other oxidation stress and metabolic abnormalities. A study in Birmingham, USA revealed that migrant Indians have higher small dense LDL compared to their white counterparts.[62] In a study in south Indians we showed that small dense LDL levels were higher in diabetic patients and even higher in diabetics with CAD (Table 18.1).[63] Small dense LDL is considered to be more prone to oxidation and conformational changes.[64]

Table 18.1: Mean levels of small dense LDL and oxidised LDL[63, 70]

Small dense LDL (mg/dl)	7.2 ± 6.8	11.1 ± 8.0*
Oxidised LDL (U/L)	26.2 ±16.6	40.1± 13.1#

* $p < 0.05$, # $p < 0.001$ compared to non-diabetic subjects

Oxidised LDL (OX-LDL)

Some studies have shown the oxidisability of LDL to be associated with early structural changes.[65] Oxidatively modified LDL, has reduced clearance by its receptors, triggering immunological changes resulting in atherosclerosis.[66] OX-LDL is found in monocyte-derived macrophages in atherosclerotic lesion but not in normal arteries.[67] It has also been suggested that OX-LDL induces smooth muscle cell proliferation.[68] An earlier study from south India[69] has shown an increase in antibodies to oxidised LDL in Indians with CAD. In a recent study we had shown that oxidised LDL increases with increase in severity of glucose intolerance (Table 18.1) and it also exhibited a strong association with IMT.[70]

LIFESTYLE FACTORS AND CAD

India is facing a rapid epidemiological transition which has led to transition in nutrition and lifestyle. Increased consumption of energy dense fast foods combined with sedentary lifestyles has increased the prevalence of diseases like diabetes and CAD. Several studies have shown an increase in the

prevalence of cardiovascular risk factors in urban areas compared to rural areas.[71, 72] In the CUPS study, proportion of subjects with diabetes and hypercholesterolaemia were higher among middle-income group compared to low-income group.[73] In the same study we also analysed the association of CAD with physical activity. When heavy grade activity was taken as reference, the odds ratio for CAD in the light grade activity was 2.42 (95% confidence interval: 1.40-4.24, p=0.011) for CAD.[74] There is increasing evidence that with changes in lifestyle prevention of CAD is possible, further, the DPP and DPS studies have clearly documented that diabetes also can be prevented by exercise and weight loss.[75-77]

CONCLUSIONS

Overall, Indians seem to be more predisposed to both diabetes and CAD. This is due to lifestyle changes with increased consumption of high energy dense foods and decreased physical activity. By adopting lifestyle changes, more of these risk factors can be modified and thereby both diabetes and CAD are potentially preventable.

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