Review
RSSDI ORATION 2003
WHY ARE INDIAN DIABETIC SUBJECTS MORE PRONE TO CORONARY ARTERY DISEASE?

V Mohan

ABSTRACT

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

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

DIABETES AND CAD

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

PREVALENCE OF DIABETES AND CAD IN INDIANS

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

The Global Disease Burden Study concluded that CAD mortality in the developing countries in 1990 to be over 9 million, of which India contributed to 2.4 million deaths, which accounts for over 25% of the all deaths reported in India [11]. Furthermore, it is also projected that in India cardiovascular disease would account for majority of the disability adjusted loss of years [DALY's] in the future (12). According to the World Bank figures, overall cardiovascular mortality in Indians has been projected to rise by 103% in men and 90% in women between 1985 and 2015 (13). Data from the native Indian population, in early 60's revealed that the prevalence of heart disease was 1.05% [14] and this has increased markedly and

Director, M. V. Diabetes Specialities Centre & Madras Diabetes Research Foundation, 4, Conran Smith Road, Gopalapuram, Chennai – 600 086. India

currently ranges from 7.6 –14.3% (Table 1) (14-23). In the rural population, the prevalence of heart disease has increased from 2.0% in 1974 to 3.8% in 1994, representing a two fold increase in the last 20 years (24, 25).

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

Reference	State	Sample size (age in years)	Year	Prevalence of CAD
Padmavathy (15)	Uttar Pradesh	1642 (>20)	1959	1.0%
Sarvotham et al (16)	Haryana	1331 (> 30)	1968	6.6%
Gupta et al (17)	Haryana	1504 (>30)	1975	4.5%
Chaddha et al (15)	New Delhi	13,723 (25-64)	1990	9.7%
Begom et al (16)	Kerala	460 (26 -65)	1995	13.9%
Singh et al (17)	Uttar Pradesh	152 (26-65)	1995	8.6%
Gupta et al (18)	Rajasthan	2212 (³ 20)	1995	7.6%
Ramachandran et al(19)	Tamil Nadu	953 (³ 40)	1998	14.3%
Mohan et al (20)	Tamil Nadu	1175 (³20)	2000	11.0%
Gupta et al (21)	Rajasthan	1123 (³20)	2002	8.2%

Chennai Urban Population Study

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

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

PRECLINICAL ATHEROSCLEROTIC MARKERS

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

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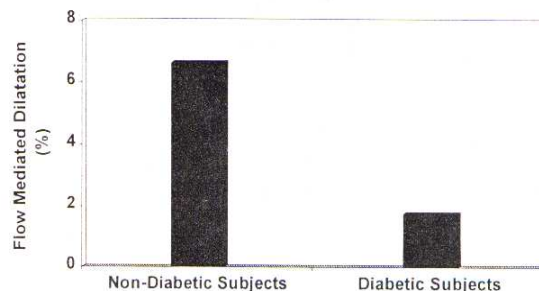

Figure 1 A : Mean FMD values in diabetic and non-diabetic subjects – The Chennai Urban Population Study (CUPS)
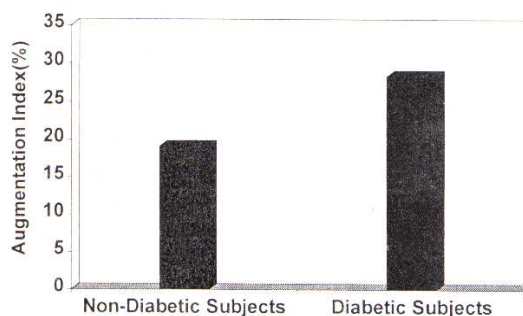

Figure 1 B : Mean AI values in diabetic and non-diabetic subjects – The Chennai Urban Population Study (CUPS)

CARDIOVASCULAR RISK FACTORS IN DIABETIC SUBJECTS

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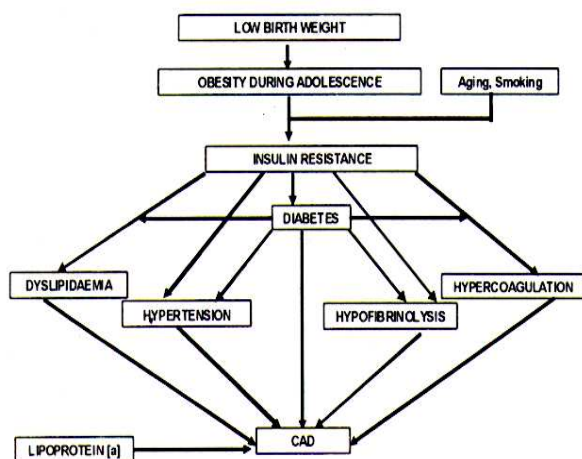

Figure 2 : Interlink of Cardiovascular Risk Factors

Hyperglycemia and CAD

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

Hypertension and CAD

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

Dyslipidemia and CAD

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

Hypercoagulation and Hypofibrinolysis and CAD

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

Lipoprotein(a) and CAD

Lipoprotein(a) is a complex of apolipoprotein (a) and LDL. Lp(a) has a striking homology and common genetic determinants with plasminogen and can competitively inhibit plasminogen activity leading to impaired fibrinolysis (44-46). Lipoprotein (a) has also been implicated in

enhanced oxidation and foam cell formation. In our study we showed that Lp(a) had an independent association with CAD in Type 2 diabetic patients (47). Several other studies have supported 4 this association [42, 43]. Recently we showed that an increase in lipoprotein (a) was associated with increase in carotid intimal medial thickening, a preclinical atherosclerotic marker (48). This suggest that Lp(a) is associated with CAD even at an early stage of atherosclerosis and thus could play a major role in the development of CAD.

Homocysteine and CAD

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

Inflammatory markers and CAD

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

CONCLUSION

Various risk factors like diabetes, dyslipidemia, hypertension, hypercoagulation, hypofibrinolysis and inflammation are associated with CAD. Some of these factors are modifiable by therapeutic interventions. Most of these factors can be modified by life style modifications like dietary modification, regular physical activity, weight reduction and cessation of smoking. Control of

CAD in diabetic patients would however require a multi-pronged approach to reduce the risk of CAD, which includes in addition to life style modifications, tight control of hyperglycemia, blood pressure and hyperlipidemia as shown in the recent Steno – 2 study (60).

REFERENCES

1. Kannel WB. Metabolic risk factors for coronary heart disease in women: perspective from the Framingham Study.Am Heart J 1987; 114:413-9.

2. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with Type 2 diabetes and in non diabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 330:229.

3. Haffner SM. Patients with type 2 diabetes: The case for primary prevention. Am J Med 1999; 23: 43S–45S.

4. Abbot RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs. women: the Framingham study. JAMA 1988; 260: 3456–60.

5. King H,Aubert RE,Herman WH. Global burden of diabetes, 1995 - 2025 - Prevalence, numerical estimates and projections. Diabetes Care 1998; 2:1414-31.

6. Pradeepa R, Deepa R, Mohan V. Epidemiology of Diabetes in India – Current perspective and future projections. J Indian Med Assoc 2002; 100: 144–7.

7. Arvind K, Pradeepa R, Deepa R, Mohan V. Diabetes & coronary artery disease Indian J Med Res 2002; 116:163-76.

8. Ahuja MMS. Epidemiology studies on diabetes mellitus in India. In. Ahuja MMS (ed). Epidemiology of diabetes in developing countries, Interprint, New Delhi. 1979; pp 29 – 38.

9. Ramachandran A, Snehalatha C, Dharmaraj D, Viswanathan M. Prevalence of glucose intolerance in Asian Indians. Urban-rural difference and significance of upper body adiposity. Diabetes Care 1992; 15: 1348-55.

10. Ramachandran A, Snehalatha C, Kapur A, et al. Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia 2001; 44: 1094 -101

11. Murray CJ. Quantifying the burden of disease: the technical basis for disability- adjusted life years. Bull WHO 1994; 72:429-45.

12. Murray CJ, Lopez AD. Alternative projection of mortality and disability by cause 1990-2020; Global Burden of Disease Study. Lancet 1997; 349:1498-504.

13. Bulato RA, Stephens PW. Global estimates and projections of mortality by cause. Washington. DC:

Population, Health and Nutrition Department: World Bank, pre-working paper. 1992; 1007.

14. Padmavati S, Gupta S, Pantulu GVA. Dietary fats, serum cholesterol levels and incidence of atherosclerosis in Delhi. Circulation 1959; 19: 849.

15. Sarvotham SG, Berry JN. Prevalence of coronary artery disease in urban population in northern India. Circulation 1968; 37: 939–53.

16. Gupta SP, Malhotra KC. Urban—rural trends in the epidemiology of coronary heart disease. J Assoc Physicians India 1975; 23:885-92.

17. Chadha SL, Radhakrishnan S, Ramachandran K, Kaul U, Gopinath N. Epidemiological study of coronary heart disease in urban population of Delhi. Indian J Med Res 1990; 92: 424-30.

18. Begom R, Singh RB. Prevalence of coronary artery disease and its risk factors in the urban population of South and North India. Acta Cardiol 1995; 50:227-40.

19. Singh RB, Ghosh S, Niaz AM, Gupta S, Bishnoi I, Sharma JP, Agarwal P, Rastogi SS, Beegum R, Chibo H, et al. Epidemiologic study of diet and coronary risk factors in relation to central obesity and insulin levels in rural and urban populations of north India. Int J Cardiol 1995; 47:245-55.

20. Gupta R, Prakash H, Majumdar S, Sharma S, Gupta VP. Prevalence of coronary heart disease and coronary risk factors in an urban population of Rajasthan. Indian Heart J 1995; 47:331–8.

21. Ramachandran A, Snehalatha C, Latha E, Satyavani K, Vijay V. Clustering of cardiovascular risk factors in urban Asian Indians. Diabetes Care 1998; 21: 967-71.

22. Mohan V, Deepa R, Shanthirani S, Premalatha G. Prevalence of coronary artery disease and its relationship to lipids in a selected population in South India – The Chennai Urban population Study (CUPS No. 5). J Am Coll Cardiol 2001; 38: 682–7.

23. Gupta R, Gupta VP, Sarna M, et al. Prevalence of coronary heart disease and risk factors in an urban Indian population: Jaipur Heart Watch-2. Indian Heart J 2002; 54: 59-66.

24. Bahl VK, Prabhakaran D, Karthikeyan G. Coronary artery disease in Indians. Indian Heart J 2001; 53:707-13.

25. Gupta R, Prakash H, Kaul V. Cholesterol lipoproteins, triglycerides, rural-urban differences and prevalence of dyslipidemia among males in Rajasthan. J Assoc Physicians India 1997; 45:275-9.

26. Shanthi Rani CS, Rema M, Deepa R, et al. The Chennai Urban population Study (CUPS) – Methodological Details – (CUPS Paper No.1). International Journal of Diabetes in Developing Countries 1999; 19: 149-57.

27. Deepa R, Shanthirani CS, Premalatha G, Sastry NG, Mohan V. Prevalence of insulin resistance syndrome in a selected south Indian population— the Chennai urban population study-7 [CUPS-7]. Indian J Med Res 2002; 115:118-27.

28. Pradeepa R, Deepa R, Rani SS, Premalatha G, Saroja R, Mohan V. Socioeconomic status and dyslipidaemia in a South Indian population: the Chennai Urban Population Study (CUPS 11). Natl Med J India 2003; 16:73–8.

29. Deepa R, Arvind K, Mohan V. Diabetes and risk factors for coronary artery disease. Current Science 2002; 83:1497–505.

30. Mohan V, Shanthirani CS, Deepa R. Glucose intolerance (diabetes and IGT) in a selected south Indian population with special reference to family history, obesity and life style factors – The Chennai Urban Population Study (CUPS 14). Journal of Association of Physicians of India 2003; 51; 771-7.

31. Mohan V, Ravikumar R, ShanthiRani S, Deepa R. Intimal medial thickness of the Carotid Artery in south Indian diabetic and non diabetic subjects :the Chennai Urban Population Study (CUPS). Diabetologia 2000; 43: 494-9.

32. Ravikumar R, Deepa R, Shanthirani CS, Mohan V. Comparison of Carotid Intima-Media thickness, Arterial Stiffness and Brachial Artery Flow Medicated Dilatation in Diabetic and Non-Diabetic Subjects. (The Chennai Urban Population Study [CUPS NO:9]. Am J Cardiol 2002; 90:702–7.

33. Reaven GM. A syndrome of resistance to insulin stimulated uptake (Syndrome X). Definitions and implications. Cardiovasc Risk Factors 1993; 3: 2 – 11.

34. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Cardiovascular risk factors clustering with endogenous hyperinsulinaemia predict death from coronary heart disease in patients with Type II diabetes. Diabetologia 2000; 43:148–55.

35. Lempiainen P, Mykkanen L, Pyorala K, Laakso M, Kuusisto J . Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. Circulation 1999; 100:123-8.

36. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335:765-74.

37. Deepa R, Shanthirani CS, Pradeepa R, Mohan V. Is the "Rule of Halves" in hypertension still valid? – Evidence from the Chennai urban Population Study (CUPS). J Assoc Physicians India 2003; 51: 153-7.

38. Syvanne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. Lancet 1997; 350 Suppl 1:SI20–S123.

39. Kulkarni KR, Markovitz JH, Nanda NC, Segrest JP. Increased prevalence of smaller and denser LDL particles in Asian Indians. Arterioscler Thromb Vasc Biol 1999; 19: 2749–55.

40. Juhan-Vague I, Alessi MC, Vague P. Increased plasma plasminogen activator inhibitor 1 levels: a possible link between insulin resistance and atherothrombosis. Diabetologia 1991; 34:457-62.

41. Schneider DJ, Nordt TK, Sobel BE. Attenuated fibrinolysis and accelerated atherosclerosis in type II diabetic patients. Diabetes 1993; 42:1-7.

42. Deepa R, Velmurugan K, Saravanan G, et al. Relationship of tissue plasminogen activator, plasminogen activator inhibitor-1 and fibrinogen with coronary artery disease in South Indian male subjects. J Assoc Physicians India 2002; 50:901-6.

43. Ramachandran A, Sathyamurthy I, Snehalatha C, et al. Risk variables for coronary artery disease in Asian Indians. Am J Cardiol 2001; 87:267-71.

44. Sandholzer C, Boerwinkle E, Saha N, Tong MC, Utermann G. Apolipoprotein(a) phenotypes, Lp(a) concentration and plasma lipid levels in relation to coronary heart disease in a Chinese population: evidence for the role of the apo(a) gene in coronary heart disease. J Clin Invest 1992; 89:1040-6.

45. Anjana Mohan, Srinivasan V, Deepa R, Mohan V. Lipoprotein (a): role in diabetes and its vascular complications. J Assoc Physicians India. 2001; 49:1100–5.

46. von Eckardstein A, Schulte H, Cullen P, Assmann G. Lipoprotein(a) further increases the risk of coronary events in men with high global cardiovascular risk. J Am Coll Cardiol 2001; 37:434-9.

47. Mohan V, Deepa R, Haranath S, et al. Lipoprotein(a) is an independent risk factor for coronary artery disease in NIDDM patients in South India. Diabetes Care 1998; 21:1819-23.

48. Velmurugan K, Deepa R, Ravikumar R, et al. Relationship of lipoprotein (a) with intimal medial thickness of the carotid artery in type 2 diabetic patients in South India. Diabet Med 2003: 20:455-61.

49. Dardik R, Varon D, Tamarin I, et al. Homocysteine and oxidized low density lipoprotein enhanced platelet adhesion to endothelial cells under flow conditions: distinct mechanisms of thrombogenic modulation. Thromb Haemost 2000; 83: 338–44.

50. Moghadasian MH, McManus BM, Frohlich JJ. Homocysteine and coronary artery disease. Arch Intern Med 1997; 157: 2301-7.

51. Chambers JC, Obeid OA, Refsum H, et al. Plasma homocysteine concentrations and risk of coronary heart disease in UK Indian Asian and European men. Lancet 2000; 355: 523–7.

52. Chacko KA. Plasma homocysteine levels in patients with Coronary Heart Disease. Indian Heart J 1998: 50: 295-9.

53. Deepa R, Velmurugan K, Saravanan G, Karkuzhali K, Dwarakanath V, Mohan V. Absence of association between serum homocysteine levels and coronary artery disease in South Indian males. Indian Heart J 2001; 53: 44-7.

54. Tousoulis D, Davies G, Stefanadis C, Toutouzas P, Ambrose JA. Inflammatory and thrombotic mechanisms in coronary atherosclerosis. Heart 2003; 89:993-7.

55. Blake GJ, Ridker PM. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. J Am Coll Cardiol 2003; 41(4 Suppl S):37S-42S.

56. Pradhan AD, Ridker PM. Do atherosclerosis and type 2 diabetes share a common inflammatory basis? Eur Heart J 2002; 23:831-84.

57. Haffner SM. Insulin resistance, inflammation, and the prediabetic state. Am J Cardiol 2003;92:18J-26J

58. Blake GJ, Ridker PM. Inflammatory bio-markers and cardiovascular risk prediction. J Intern Med 2002; 252:283- 94.

59. Abrams J C-reactive protein, inflammation, and coronary risk: an update. Cardiol Clin 2003; 21:327-31

60. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383-93