Macrovascular Component of Diabetes Atherosclerosis and Insulin (CUPS-18)

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Atherosclerosis

Atherosclerosis, a complicated multifactorial pathological process, affects the large and medium sized arteries resulting in macrovascular disease. Though the end-points of atherosclerosis are well defined, there is no clear explanation for the pathophysiology of atherosclerosis. However, the atherosclerotic process could be sequenced as functional changes and structural changes of the artery. The first to occur would be functional changes in the arteries leading to the loss of elasticity. Structural changes like fatty degeneration and foam cell formation occur later leading to intimal medial thickening, plaque formation, finally to clogging of the artery interfering with blood flow. The plaque eventually ruptures with consequent intraluminal thrombosis, which results in the end-points like coronary artery disease [CAD], cerebrovascular disease [CVD] and peripheral vascular disease [PVD]. [1] CAD and CVD are indeed the first and second causes of mortality worldwide.[2]

Macrovascular disease and diabetes

Macrovascular disease is one of the major causes of mortality and morbidity in diabetes, and several studies indicate that diabetic patients have 2-5 times higher death rates due to atherosclerotic disease than non-diabetic individuals.[3-5] The prevalence of all manifestations of coronary artery disease like myocardial infarction, angina and sudden death are higher in patients with type 2 diabetes mellitus.[6-7] In fact studies have reported CAD, to be present even at the time of diagnosis of diabetes and indeed even in prediabetic stages like impaired glucose tolerance [IGT].[8] It has been suggested that there is an eight years decrease in life expectancy due to diabetes.[9] The protective effect observed among pre-menopausal women disappears after diabetes sets in[10] and in fact diabetic women often have a higher risk for CAD than diabetic men.[11]

CVD and diabetes: Prospective studies have shown diabetes to be a major risk factor for cerebrovascular disease. Mortality due to stroke is twice as high among subjects with diabetes. A follow up study on 1,160 subjects in Minnesota, (mean follow up years: 3.4 years) concluded that diabetes is one of the predictors of future cardiovascular event.[12] Furthermore, the risk for reinfarction is shown to be higher in diabetic subjects compared to non-diabetic subjects.[13] A recent study on subjects who underwent vascular surgery reported diabetes to be a major risk for adverse outcomes like stroke and hospital death.[14]

CAD and diabetes: In the 1980's Kannel et al[3] was the first to demonstrate that diabetic men and women have a 3.5 to 4 fold higher risk of CAD mortality compared to non-diabetic women in the Framingham study. Follow up data for upto 24 years confirmed the higher mortality rates among diabetic subjects and also a cumulative effect of age and diabetes.[15] Co-existence of multiple risk factors among diabetic subjects has been shown to dramatically increase the mortality rates compared to non-diabetic subjects. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) study showed that diabetic subjects without prior CAD had a similar risk for developing CAD as non-diabetic subjects with prior CAD.[4] This was confirmed again by the studies by Haffner et al[5,16] who proposed that the clock for CAD starts ticking from the stage of IGT itself.
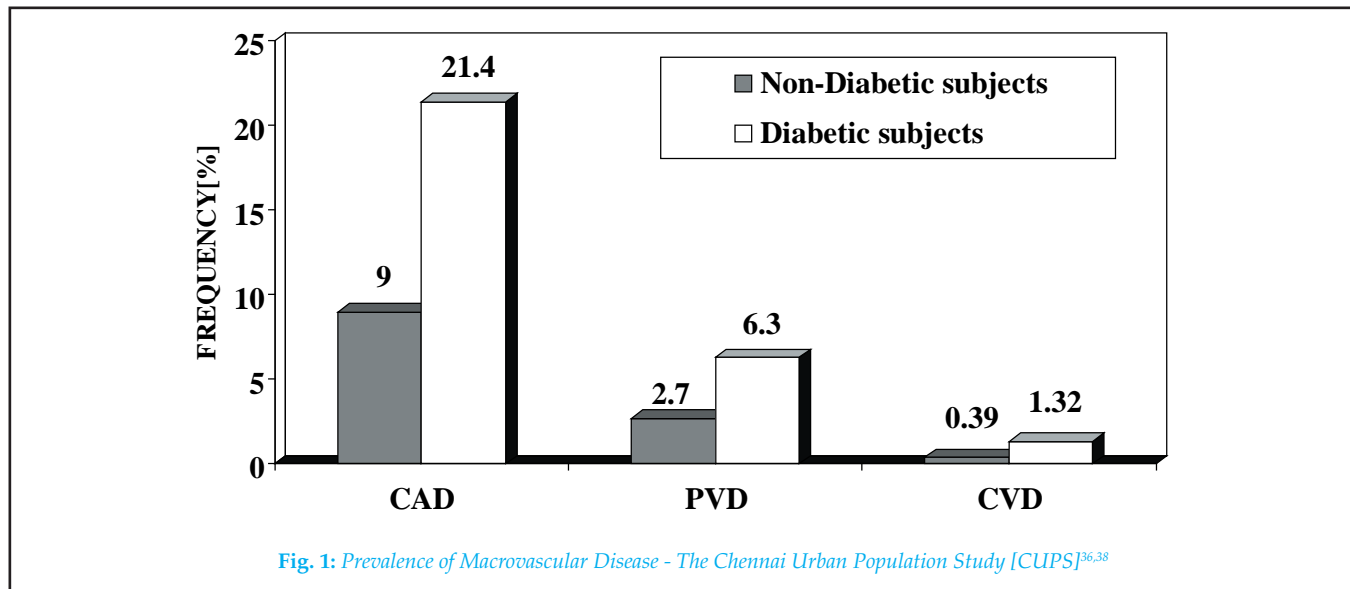
PVD and diabetes: The prevalence of PVD has been shown to be higher among diabetic subjects compared to age and sex matched non-diabetic subjects.[17,18] Earlier studies from USA, UK, Greece, and the Netherlands have clearly shown that diabetic subjects have a higher risk for PVD compared to non-diabetic subjects.[19-21] Studies on Asian Indians have also demonstrated a similar higher prevalence of PVD among diabetic subjects.[22] However, the overall prevalence of PVD in Indians was lower than that reported in western studies.[22] Other risk factors for PVD in type 2 diabetic subjects are high triglycerides, low HDL cholesterol, hypertension and smoking.[23]

Epidemiology of diabetes and cardiovascular disease in Indians

Earlier studies in Western countries have confirmed that the prevalence of diabetes among migrant Indians is significantly higher than in the indigenous populations.[24,25] In the 1970's diabetes among urban Indians was shown to be 2.1%, [26] this rose to 8.0% in 1982[27] and is currently 12% according to the recent National Urban Diabetes Study.[28] Recent studies from different regions of the country have shown a rising prevalence of diabetes.[29,30] Projections by WHO,[31] have highlighted that India already leads the world in the prevalence of diabetes and would continue to hold the top position in the forthcoming years and numbers are expected to increase to 80.9 million by the year 2030.[32]

The Chennai Urban Population Study (CUPS)

To determine the prevalence of diabetes and macrovascular disease in South Indians, we undertook a population-based study in urban South Indians called the Chennai Urban Population Study (CUPS).[33] Briefly, 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 greater than 20 years living in these two colonies were requested to participate in the study. Of the total of 1399 eligible subjects (age ≥ 20 years), 1262 (90.2%) participated in the study. The study subjects underwent a glucose tolerance test (GTT)

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Fig. 1: *Prevalence of Macrovascular Disease - The Chennai Urban Population Study [CUPS][36,38]*

and were categorized 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.[33,34]

Prevalence of diabetes: Overall, 12% of the total population had diabetes and on age standardization this reduced to 9.3%. Of the 152 diabetic subjects identified in the CUPS study, 7.2% were known diabetic subjects and 4.8% were undiagnosed diabetic subjects. The prevalence of impaired glucose tolerance was 5.9% (age standardized prevalence 5.0%). This means that 1 out of six persons in urban areas in India will have some degree of glucose intolerance. In adults aged 40 years and above, one out of four individuals will have glucose intolerance.[35]

Prevalence of CAD: The overall crude prevalence rate of CAD was 11.0%, and the age-standardized figure was 9.0%. The prevalence of CAD was higher among diabetic subjects [21.4%] compared to 14.9% in those with IGT and 9.1% in subjects with normal glucose tolerance[36] (Figure 1). Indeed the risk for CAD seemed to increase even at the stage of IGT and was similar to that noted among newly diagnosed diabetic subjects[37].

Prevalence of PVD: PVD was present in 3.2% of the study population. The age standardized prevalence in the population was 2.0%. 2.7% of the normals, 2.9% of the subjects with IGT and 6.3% of the diabetic subjects had PVD [Figure 1]. Prevalence of PVD in newly diagnosed diabetic subjects was 3.5% compared to 7.8% in known diabetic subjects.[38]

Prevalence of CVD: Self reported stroke was assessed in the CUPS population. The overall prevalence of stroke was 0.63% and in diabetic subjects it was 1.32% which was three times higher than that observed in normal subjects (0.39%) [Figure 1].

Preclinical atherosclerotic markers: Macrovascular disease is one of the clinical end points of atherosclerosis, which in its earlier stages, as discussed earlier, involves both structural and functional changes in the arteries. Structural changes can be studied using non-invasive techniques like high-resolution ultrasound by measuring Carotid Intimal Medial Thickness[IMT] while functional changes can be studied by looking at flow-mediated dilatation or arterial stiffness. These pre-clinical atherosclerotic markers have gained wide recognition as they are useful surrogate markers for CAD and can also be used in studies on prevention and intervention of CAD.[39,40]

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 compared to normal subjects.[40] 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 in CUPS [Figure 2].

We also observed that the diabetic subjects had increased IMT at every age point compared to their non-diabetic counterparts.[41] Further, the newly diagnosed diabetic subjects had significantly higher IMT values compared to normal subjects, but significantly lower compared to known diabetic subjects. Further analysis of the data revealed that diabetes per se was an important risk factor for increase in IMT.[41]

We next looked at functional changes in arteries by studying endothelial dysfunction and arterial stiffness. Endothelial dysfunction was measured as flow-mediated dilatation (FMD) of the brachial artery using high-resolution B mode ultrasonography. Flow-mediated dilatation (FMD) was found to be reduced in diabetic patients (2.1 ± 2.95%) compared to age and sex matched non-diabetic subjects (6.64 ± 4.38%, p < 0.0001).[42]

Arterial stiffness was measured by the Augmentation index of the radial artery using the Sphygmocor machine and was found to be significantly greater in diabetic subjects (27.48 ± 7.41%) compared to age and sex matched non-diabetic subjects (19.10 ± 8.19%), p < 0.0001.[42]

Earlier studies on intimal medial thickness on subjects with diabetes clearly demonstrated that atherosclerosis manifests 2 to 3 decades earlier among diabetic subjects

Fig. 2: *Prevalence Of Carotid Atherosclerosis - The Chennai Urban Population Study [CUPS][41]*
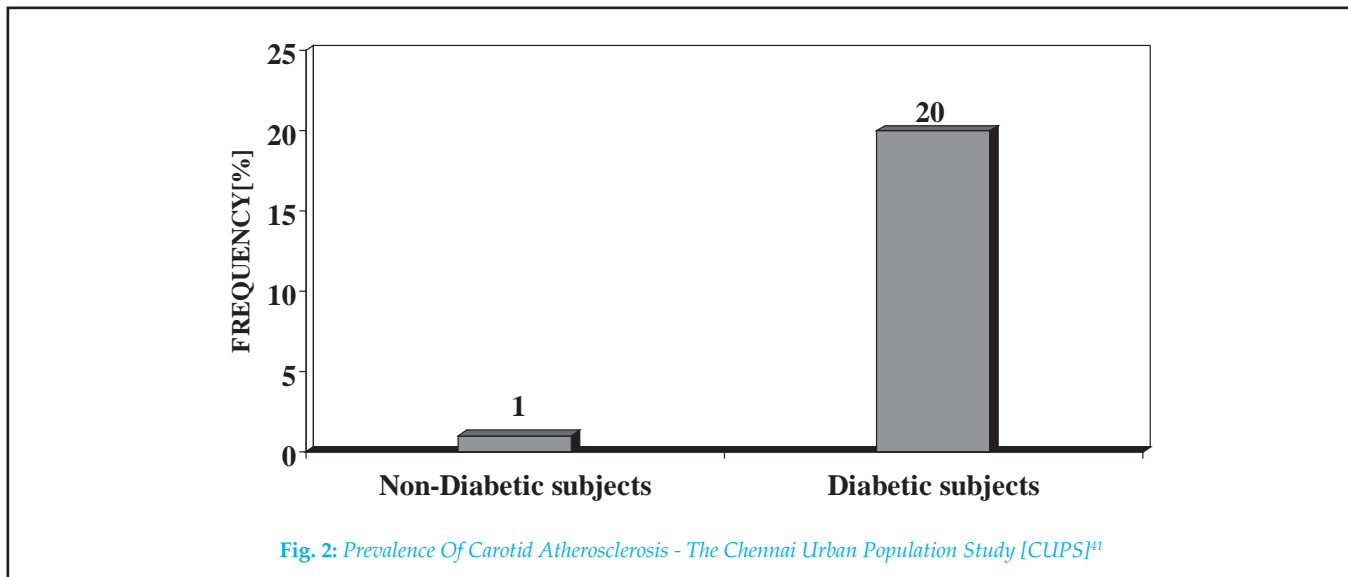
compared to non-diabetic subjects.[43] The Cardiovascular Health Study also showed higher prevalence of preclinical atherosclerosis compared to normals.[44]

Insulin and atherosclerosis

Accelerated development of atherosclerosis in diabetes has been the subject of intense study in the past two decades which has enhanced our knowledge of both causative factors as well as the pathophysiology.[45] These studies have improved our understanding of the pathogenic mechanisms of atherosclerosis and the trigger mechanisms that lead to acute clinical events in diabetes. During the last two decades the role of insulin in atherosclerosis has been a subject of heated debate.

The association of insulin and atherosclerosis could be considered under two heads. The first is the contribution of increased endogenous insulin production i.e., hyperinsulinemia to atherosclerosis; second the beneficial effect of exogenous insulin in preventing cardiovascular deaths. These will be discussed in detail in the sections below.

Hyperinsulinemia, insulin resistance syndrome and atheroslcerosis: Insulin resistance and the compensatory increase in insulin secretion bring about a state of chronically increased insulin and glucose levels in the blood (hyperinsulinemia and hyperglycemia), which are predecessors for both diabetes and cardiovascular disease. The term insulin resistance syndrome includes a host of abnormalities, including hypertension, hyperinsulinemia, hypertriglyceridemia, increased levels of small dense low density lipoprotein (LDL), and low high density lipoprotein (HDL), and hypercoagulability. These abnormalities constitute the Reaven's syndrome otherwise named as Insulin Resistance Syndrome, or Pluri Metabolic Syndrome.[46]

Hyperinsulinemia and atherosclerosis: There is ample evidence to suggest a direct role of hyperinsulinemia in the development of atherosclerosis through stimulation of vascular smooth muscle cell proliferation and arterial wall lipid deposition.[47] Insulin has also been implicated as an indirect cause of atherogenesis as it promotes the

development of hypertension and dyslipidemia.[48,49] The Helsinki Policeman Study, which followed up 970 non-diabetic men who were free of coronary artery disease revealed fasting insulin to be a predictor for CAD.[50]

Insulin resistance and clustering of risk factors: Although insulin resistance syndrome is a cluster of various abnormalities, a concomitant presentation of all components of the syndrome is rare. Therefore, in the view of most experts, three components are sufficient for defining the syndrome. The insulin resistance syndrome seems to explain a major part of the CAD occurrence.[51]

Insulin resistance syndrome in Indians

Hyperinsulinemia,[52] insulin resistance[53] and other components of metabolic syndrome[24,25,54] have been shown to be more prevalent among Asian Indians. The prevalence of Insulin resistance syndrome (IRS) defined using the European Group of Insulin Resistance (EGIR) criteria was found to be 11.2% among South Indians.[55] The definition for IRS was as follows: - insulin resistance calculated using the Homeostasis Model Assessment (HOMA IR), >1.93, [being the 75th percentile of the total population) in combination with at least 2 of the following conditions; hyperglycaemia, hypertension, dyslipidaemia or central body obesity.[34]

Factor analysis, a complex statistical technique has been extensively used for identifying clustering of the insulin resistance factors. Initially Meigs[56] showed that the IRS components tend to cluster together. Later, using the same technique, Lempiainen et al[57] demonstrated that this cluster predicts CAD in non- diabetic population followed up for 7 years. Studies conducted on type 2 diabetic subjects[51] and the insulin resistance syndrome cluster was also shown to predict death.[58] A similar clustering of the factors contributing to the insulin resistance syndrome has also been shown among native Indians.[59] In the CUPS study also, we observed that the metabolic abnormalities tend to cluster and that subjects with more than one metabolic abnormality had a higher prevalence of CAD compared to subjects with a single metabolic abnormality.[60] However, the role of hyperinsulinemia per se in atherogenesis is still a debatable issue and the association is seen mostly in middle aged men and not in women or in elderly men.[51]

Abnormalities of coagulation and fibrinolysis in insulin resistance: Insulin resistance is associated not only with the classic cardiovascular risk factors of hypertension and dysplipidaemia, but also with disorders of coagulation and fibrinolysis. Increased PAI-1 levels have been shown to be associated with higher insulin and proinsulin levels.[61] Patients with insulin resistance syndrome and diabetes mellitus tend to have increased PAI-1 levels. In our study on subjects with and without diabetes, PAI-1 and fibrinogen were higher among diabetic subjects compared to non-diabetic subjects.[62]

Inflammation and insulin resistance: More recently, chronic subclinical inflammation has been proposed as a part of the insulin resistance syndrome. Evidence from various studies has shown that inflammatory markers predict the development of diabetes.[63] In both insulin resistance and atherosclerosis, the acute-phase response is enhanced. Studies of the factors that regulate the acute-phase response have yielded consistent results implicating cytokines and growth factors in the pathophysiology of insulin resistance and atherosclerosis. This includes markers like C-reactive protein, interleukins and tumour necrosis factor.[64-67]

Insulin therapy and atherosclerosis

Diet and exercise are the initial therapy for Type 2 diabetic patients in whom insulin resistance is an important component of the altered glucose homeostasis. Both these forms of treatment improve the peripheral insulin sensitivity as well as the pancreatic beta cell function. If these measures do not result in the desired improvement in glycemic control, then oral agents or insulin are added. Both these forms of therapy are known to improve insulin action.

Therapeutic role of insulin – clinical benefits: Infusion of insulin has been shown to have remarkable benefit in subjects with myocardial infarction.[68-69] The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction[DIGAMI] Study compared long term all cause mortality in 306 diabetic patients who received intensive treatment to 314 on conventional therapy.[69] The mean follow up period was 3.4 years. The study revealed a reduction in mortality by 30% in the group which received glucose insulin infusion initially, followed by four times daily insulin for three months. Recent studies have demonstrated that continuous insulin infusion reduced the mortality significantly compared to subcutaneous insulin.[70]

Therapeutic role of insulin – mechanism: Apart from controlling hyperglycaemia insulin also intervenes with many other metabolic and inflammatory pathways to prevent atherosclerotic endpoints. Plasma free fatty acids, which are increased due to enhanced catabolism, would induce inflammation and also worsen the clinical outcomes.[71] Normalizing free fatty acids by exogenous insulin could yield significant benefits.[68] Suppression of PAI-1 production by insulin is of benefit as this would increase clot dissolution.[68,72] There are many other potential benefits of insulin, mainly inhibition of pro-inflammatory early growth response gene-1(Egr-1) and tissue factor indicating its anti-inflammatory properties.[68,73] The basic mechanism by which insulin acts as an anti-inflammatory factor is by enhancing nitric oxide

production.[74] The vasodilatatory effect of insulin could also be one of the reasons for its favourable effects.[75]

Conclusions

It is clear from the literature that macrovascular disease is a common complication of diabetes, the link being insulin resistance and hyperinsulinemia. On the contrary exogenous insulin therapy in diabetic subjects has shown to be beneficial. Furthermore, continuous insulin infusion is more advantageous than subcutaneous insulin. Appropriate use of insulin could help in achieving good diabetic control. Good control of diabetes, hypertension, hyperlipidaemia and obesity coupled with lifestyle changes can help to prevent atherosclerosis in diabetic patients.

Acknowledgement

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