Reflections on Cardiac Complications of Diabetes Mellitus

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Throughout the world, incidence of diabetes is on an increase. On its own, it is presently ranked seventh as a cause of mortality in the West. But diabetes is known as a disease of complications. Apart from those which are specific to the condition, it promotes mortality in such related disorders as hypertension, stroke and above all, ischaemic heart disease. When these are taken into account, diabetes may be reckoned next to cardiovascular disorders and cancer as a cause of human mortality.

At the Joslin Clinic, USA, cardiac disorders accounted for death in 6-10% of diabetic patients during the last decade of the 19th and first two decades of the present century. Following availability of insulin and a number of antibiotics for treatment of potentially fatal metabolic and infective complications and consequent increase in longevity, there was a steep rise in the incidence of coronary heart disease (CHD). This alone accounted for over 40% of deaths in patients with diabetes during the 40's, soaring to above 50% in the sixth decade of life. This was much higher as compared to the prevalence of around 30% in the general population. Currently, in spite of a visible decline of mortality from CHD among the latter, over 70% of diabetic patients of either sex, above 65 years in age, die from disorders of the heart.

While association of angina pectoris with diabetes was appreciated in 1883 by Vergely [2] and in 1885 by Bose [3], sclerotic changes in coronary arteries were first highlighted by Brunton in 1907 [4] while discussing the heart in relation to diabetes. Following the firm observations of higher incidence of CHD in diabetes by Levine [5], a vast amount of literature and a large variety of statistical data on epidemiology, pathogenesis, clinical features, course, complexities, prognosis and management of cardiac complications of diabetes have been generated from various parts of the world. Yet, the exact mechanism for excess deaths from this cause so far remains to be elucidated.

Until recently, CHD was the only form of cardiac disorder that was known to be promoted by diabetes mellitus. In 1967, we reported on paroxysmal cardiogenic dyspnoea in 5 patients of diabetes in the absence of hypertension or any clinical or electrocardiographic evidence of ischaemic heart disease (IHD). Diabetic cardiomyopathy was proposed, to be the possible mechanism for left ventricular insufficiency in these patients [6]. Little cognisance was given to this suggestion until necropsy findings of Rubler [7], angiocardiology studies of Hamby [8] and comprehensive observations of Regan and co-workers [9] were published 5 to 10 years after our preliminary report. Similarly, although cardiac autonomic (vagal) neuropathy in diabetes was first envisaged by Eichorst way back in 1892 [10] and more comprehensively dealt with by Rundles in 1945 [11], its impact in clinical cardiology was not generally appreciated until emphasised by Wheeler and Watkins [12] as well as Ewing and co-workers [13] in 1973. Since then (1980 onwards), diabetes related cardiac disorders have been generally classified as due to (1) premature and more extensive atherosclerotic coronary artery disease (2) cardiomyopathy and (3) cardiac autonomic neuropathy. CHD is by far the most outstanding of the three, while the importance of the other two modes of cardiac afflictions may be principally because of their role in modification of the clinical characters and the progress of the major manifestations of ischaemic heart disease.

Outstanding features of CHD in patients with diabetes [14, 15] as compared to the non-diabetic population are briefly summarised as follows:

Incidence of CHD among diabetics is largely unrelated to duration, severity and mode of treatment as it is increased even in subjects with IGT, particularly in those with hyperinsulinaemia. Relative incidence is higher at a younger age and in the female sex. Painless infarct is 20-40% more frequent in diabetic patients. Angina pectoris, both pre and post myocardial infarction (MI) is relatively less frequent. During stress (Treadmill) test, pain is less often associated with ST-T changes (30 vs 70%). Further, silent ischaemia is detected more frequently and appreciation of pain is less frequent (5 vs 30%) in diabetic subjects during the course of continuous monitoring.

Angina may be expressed, instead of pain, by a sense of fatigue, breathlessness or nausea and MI by CHF, arrhythmias, vomiting or ketoacidosis (4%).

Acute myocardial infarction is beset with 2-4 fold in- total cholesterol and LDL-c were brought down...
in increase in the incidence of complications such as CHF well-nourished and normalised in the undernourished, (80%), shock (25%) and rupture of myocardium (6%).

Hospital mortality between day 2-7 of acute MI in diabetics is twice as high as compared to non-diabetics while it is nearly three times higher in course of the following two months, particularly so in cases with poor control of diabetes. Subsequent attacks are more frequent and are associated with greater mortality, so that 5 years survival may be as low as 26% compared to 79% in the non-diabetic population. Differences are wider in case of overweight middle aged women than in men.

There is a higher incidence of sudden death, 1.8 times in men and 3 times in women, possibly as manifestation of IHD.

Coronary angiography reveals more frequent involvement of left main artery, triple vessel disease and more extensive involvement of the arteries extending further into their intra-mural course. More frequent stenotic lesions in the main vessels and vasculopathy of terminal arteries and arterioles are notable at necropsy. Not withstanding these facts, bypass surgery may be as useful in most patients as in non diabetic subjects with CHD.

Our main interest has been in the analysis of geographic and ethnic variations in the incidence of CHD in diabetes, its contribution to mortality and its association with dyslipidaemias as compared to changes in haemorrhology and coagulation factors.

During the 50's and 60's, coronary heart disease was observed in 40% of diabetic patients in USA [16] as compared to 1.6% in Pakistan [17] and 2.4% in China [18]. While in the West over 50% of diabetic patients died of CHD, only 12-20% died of the same complication in Japan [19], India and other developing countries of the East. The differences cannot be ascribed fully to racial or genetic factors as Japanese living in Hawaii islands and Indians who migrated to South Africa, USA and UK have a similar or even higher incidence of CHD than their Caucasian compatriots[22]. Nutritional status and dietary factors apparently play important roles in these populations although ethnicity may be more important in the case of Pima Indians. Our observations in lean and undernourished diabetic patients below 50 years of age, revealed lower incidence of MI, coronary-probable and coronary-possible status (2.15%) compared to 18% in age and sex matched patients with better nutritional status. Hypercholesterolaemia and hypertriglyceridaemia were twice as common in the latter at the untreated state [23]. While with treatment, levels of total cholesterol and LDL-c were brought down in well-nourished and normalized in the undernourished, VLDL-c remained higher than normal in either groups, more so in the former [24]. Differences in levels of HDL-c were not significant indicating a lesser role of this protective factor in the incidence of CHD in subjects with diabetes.

Incidence of CHD in diabetes, although always higher than the rest in any particular situation, varies according to the frequency observed in the background population. Although, known risk factors like hypertension, familial hyperlipidaemias and smoking, compound the risk of CHD in patients with diabetes, hyperglycaemia per se has an important role to play through glycosylation of key cellular and circulating proteins, modification of rheological, platelet and lipid peroxidation factors. The role of insulin resistance in NIDDM and hyperinsulinaemia (endogenous or therapeutic) in subjects with IGT and diabetes of either types has to be reckoned as promoting factors for coronary atherosclerosis [25].

Changes in dietary habits of migrant Japanese and Indian subjects from traditional diets to those lacking in fibre and carbohydrates and containing more saturated fats as well as omega-6-polyunsaturated fatty acids may be primarily responsible for a higher incidence of CHD. Primary prevention strategy has to be planned taking the above into consideration. Consumption of low-fat diets richer in monounsaturated and omega-3-fatty acids as found in mustard oil and fish are most likely to be protective.

**Diabetic cardiomyopathy**, first suggested by us in 1967 on the basis of observations of 5 subjects [6] was subsequently expanded to cover 14 by 1974 [29] and 23 by 1976 [30]. Paroxysmal cardiogenic dyspnoea was noted in 11, congestive or left heart failure in 8, papillary muscle dysfunction in 3 and cardiac enlargement (left ventricular dilatation) in 2 of these patients. Conduction defects such as right bundle branch block (RBBB) and left anterior hemiblock (LAHB) were more frequent in patients with the evidence of diabetic cardiomyopathy. By 1980, we documented myocardial dysfunction on assessing systolic time intervals and echocardiography. Sample of tissue obtained by endomyocardial biopsy were subject to detailed histological examination in collaboration with Prof. A.K. Das of JIPMER, Pondicherry. Reversibility of both systolic and diastolic dysfunction of...
myocardium seen in young patients with relatively recent onset of diabetes and in patients with symptoms following establishment of control led us to suggest that metabolic factors were relatively more important in the pathogenesis of the syndrome than microangiopathy [31]. This is corroborated by observation of Regan and Lyons [9] and Factor et al [32].

Clinical and experimental observations in Pondicherry, [33] and in other parts of India and abroad have documented disorders of systolic contraction, diastolic compliance and histochemical and structural changes in the myocardium in subjects of diabetes in the absence of ischaemia due to coronary heart disease and thus have established the concept of typical cardiomyopathy as a complication of diabetes. Yet, cardiomyopathy syndrome may be mimicked by coronary artery disease with multiple small infarcts as documented by necropsy in a small proportion (16%) of cases diagnosed as non-coronary cardiomyopathy [34].

The contribution of cardiomyopathy to higher incidence of CHF and pump failure in diabetic patients with acute myocardial infarction and the possibilities for partial amelioration of the same by special attention of the cardiologists.

REFERENCES