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Cardiovascular disorders in Diabetes

Authors
Dr Santosh Kumar[1], Dr R.P.Gupta[2], Dr B.P.Singh[3]
[1]Assistant Professor Deptt. of Biochemistry Nalanda Medical College, Patna
[2]Prof.& Head Deptt. of Biochemistry Nalanda Medical College, Patna
[3]Prof.& Head Deptt. of Cardiology I.G.I.M.S. Medical College, Patna

Individuals with diabetes mellitus, both NIDDM and IDDM are at an increased risk for cardiovascular morbidity and mortality compared to non-diabetic subjects. The cardiac dysfunction in diabetes can be broadly classified as:

- Atherosclerotic coronary heart disease
- Cardiac autonomic neuropathy
- Diabetic cardiomyopathy

In this review, we shall discuss briefly about the various mechanisms involved in cardiac dysfunction.

Atherosclerotic coronary heart disease

Diabetes in an independent risk factor for developing coronary artery disease (CAD)[1]. The overall prevalence of CAD is as high as 55% for adults with diabetes compared with a prevalence of 2-4% in general population. Data from Framingham Heart Study[2] clearly demonstrates the increased risk and poor prognosis of, cardiac disease in diabetes. Mortality due to CAD is twice more common in diabetic men and quadrupled in diabetic women compared to their counterparts. The prevalence of angina, myocardial infarction and sudden death[3] are more common in diabetics. Table 1 summarizes the quantum increase is major cardiovascular events due to CAD in diabetics compared to non-diabetics.

Table 1 Increased prevalence of MACE in diabetics compared to non-diabetics

Incidence (Event)	Increase in prevalence in diabetes	
	Men	Women
Angina	60%	90%
Myocardial infarction	50%	150%
Sudden death	50%	300%

Figures indicate percentage of increase of IHD in diabetics.

It is notable that women with diabetes carry a 2-3 fold higher risk for mortality and morbidity due to cardiovascular problems compared to their non-diabetic counterparts. There are also interesting features of CAA in diabetic subjects compared to non-diabetics and these summarized in Table 2.

Table 2 Special features of CAD in diabetes mellitus
(Thanikachalam et al., personal communication)

	Diabetes	Non-diabetics
Incidence of CAD	55%	2-4%
Expression	2-3 Vessel disease	Single vessel disease
Left main coronary artery disease	13%	6%
Lesions	Multiple stenosis 50% length lesions	Single stenosis 10% length lesions

Unique features of CAD in Asian Indians

The prevalence of IHD in Indians is higher than any other population worldwide. It is 2-3 times

higher in Migrant Indians compared to Americans and Europeans, and 4-6 times higher than Chinese and Japanese population[4].

It is quite disturbing to note that CAD prevalence was high even in general population. The prevalent rates of CAD based on resting ECG's (Minnesota Coded) are shown in Table 3.

Table 3 Prevalence of IHD
(Mohan et al.,)

Event	No./1000 Population
Myocardial infarction (Q waves)	42/1000
Ischaemia (ST-T Changes)	136/1000
Total IHD	178/1000

The Prevalence of CAD compared to previous surveys in India Shows that there is constant increase in the rates, which is probably due to rapid changes of lifestyle in the population. Why is there excess of CAD in Indians? It is due to increase in westernization i.e. decreased physical activity, change in diet pattern or lifestyle. Or is it really due to ethnic differences and increased genetic susceptibility. The concept of genetic susceptibility lead to further research on Lipoprotein (a) (or LP (a) for short) which is found to be associated with premature atherosclerosis.

2. Premature atherosclerosis and role of LP (a) cholester1: CAD occurs at younger age in Indians" and the age at onset often ranges from 25-39 years, whereas it rarely occurs below the age of 40 years among Europeans. The severity of CAD i.e., the extent of the atheroma is also greater in Asian Indians[7].

Recent studies have reported that elevated levels of LP (a) – Lipoprotein (a) could predispose to CAD in young patients with no other risk factors. LP (a) is considered as a "Deadly cholesterol". Levels of LP (a) show a 10 fold difference between populations and a 1000 fold difference between individuals. It is not only associated with prematurity of CAD but also contributes to the severity and progression of CAD. Patients with higher LP (a) levels have recurrent myocardial infarction and poor survival rate after myocardial infarction. The outcome of CABG and PTCA in these patients is also poor. LP (a) has potent atherogenic properties due to structural resemblance of its apoprotein Apo (a) to plasminogen, which may interfere with plasmin generation and therefore fibrinolysis.

We performed detailed studies on LP (a) levels in three groups of subjects (i) Healthy controls (ii) NIDDN without CAD and (iii) NIDDM with CAD. The results are shown in Table 4.

Table 4 LP (a) levels different study groups
(Mohan et al.,)

	Healthy Controls (n=88)	NIDDM without CHD (n=48)	NIDDM with CHD (n=33)
LP (a) levels Mg/dl (Mean±SD)	23.7±16.7	23.1±19.9 (P<0.01)	40.5±34.0

It is clearly seen that LP (a) levels are elevated in patients with diabetes and CAD. It is also notable that there is no major difference in the levels between diabetic and non-diabetics without CAD, showing that diabetes does not alter the LP (a) levels and hence appears to be an independent risk factor for CAD unlike other lipid abnormalities which are largely influenced by the diabetic status.

3. Other cardiovascular risk factors

a. Hyperinsulinemia: It had been earlier suggested that raised plasma insulin levels with insulin resistance appears to be a atherogenic factor[8].

High insulin levels have shown to:

• Stimulate cholesterol synthesis in smooth muscle cells and macrophages of the arterial walls.

• Stimulate the proliferation and migration of smooth muscle cells.

• Enhance the binding of LDL to smooth muscle cells and macrophages. These mechanisms lead to atheroma formation."

Proinsulin and insulin like molecules (split products)[10] are now measured by radioimmun-oassay and have been shown to be probably better associated with the risk in NIDDM patients.

b. Fibrinogen levels: Diabetes is associated with several defects of coagulation and fibrinolysis. Fibrinogen levels" are increased in diabetic subjects increasing the risk for coronary artery disease.

c. Plasminogen activator inhibitor (PAI-1) PAI-is an important inhibitor of fibrinolysis. Raised levels of PAI-1 are seen in NIDDM subjects and these may have an important role in atherogenesis.

4. Microalbuminuria: Microalbuminuria and proteinuria are now recognized as independent markers of increased cardiovascular risk in subjects with diabetes[12]. It is postulated that microalbunimuria is a marker for endothelial injury that initiates atherosclerotic process. It has been found that microalbuminuric diabetic subjects, have a higher risk of hypertension, increased levels of triglycerides, LP (a), fibrinogen and PAI-1[13] and probably the combination of various factors may be responsible for the increased cardiovascular problems.

5. Smoking: Cigarette smoking is a risk, factor for cardiovascular complications in both diabetic and non-diabetic people. Although the relative risk of smoking is comparable in both groups, the absolute risk contributed by smoking is greater in diabetic patients. The interactions between diabetes and smoking on deaths from CAD were studied in MRFIT study[14]. The data based on 10th year mortality per 1000 subjects are given below (Table 5).

Table 5 Risks of smoking in diabetics vs. non-diabetics

	Non-smoking (a)	Smoking (b)	Relative of smoking S	
			Relative (b/a)	Attributable (b-a)
Non-diabetics	10.1	23.9	2.4	13.8
Diabetics	44.5	68.7	1.6	23.2

5. Hyperlipidaemia: Hyperlipidaemia has been found in approximately 50% of all diabetic patients. In diabetic patients the lipid abnormalities include low HDL cholesterol, elevated VLDL, elevated LDL and triglycerides which contribute to the cardiovascular risks. In addition, there are often alterations in the composition of the apolipoprotein.

Cardiac autonomic neuropathy

The development of symptomatic autonomic neuropathy in diabetic patients is an ominous sing with mortality over 50%, 3 years after its onset. Sudden cardiac deaths are responsible for upto one third of these deaths. Generally, parasympathetic nerve fibers are affected first, leading to a relative increase in sympathetic tone, that results in resting tachycardia and attenuation of the expected increase in heart rate and blood pressure with exercise. An absence of parasympathetic tone may also worsen ischemia. Sympathetic nervous system dysfunction is usually evident within 5 years of the diagnosis of parasympathetic dysfunction is usually evident within 5 years of the diagnosis of parasympathetic dysfunction. Postural hypotension is the classical clinical manifestation of sympathetic dysfunction.

Heart rate tests (Parasympathetic)

• Heart rate response to Valsalva
• Heart rate variation during deep breathing.
• Heart rate response to standing.

Blood Pressure tests (Sympathetic)

• Postural hypotension
• Blood pressure response to sustained hand grip.

We studied a consecutive series of NIDDM patients. Abnormalities of autonomic function tests were detected in 33.7% of NIDDM patients. There was an increase in prevalence of autonomic dysfunction with age and duration of diabetes. The prevalence was 28.2% with 5 years duration of diabetes which increased to 56.2% after 16-20 years duration. Multiple logistic analysis showed a strong correlation of autonomic neuropathy with proliferative diabetic retinopathy and peripheral neuropathy.

Diabetic cardiomyopathy

Diabetes can adversely affect myocardial function in the absence of demonstrable atheroma affecting the coronary arteries. The main manifestations are

congestive heart failure (CHF), subclinical abnormalities of left ventricular contractility. This has led to the concept of a specific cardiomyopathy associated with diabetes called diabetic cardiomyopathy.

Rubler first showed CHF in diabetic patients without atherosclerotic, valvular, congenital, hypertensive or alcoholic heart disease. The role of diabetes in development of CHF was found in the Framingham Heart Study. In this prospective study of 5000 individuals over an 18 year follow up period, the frequency diabetic cohort, while it was fivefold increased in diabetic women.

Pathogenesis of diabetic cardiomyopathy

• Myocardial enlargement.
• Myocardial hypertrophy and fibrosis.
• Increased basement membrane thickness.
• Microaneyrysms, micro vascular narrowing leading to microangiopathy.
• Abnormal calcium uptake by sarcoplasm.

Diabetic cardiomyopathy involves abnormalities of both systolic and diastolic dysfunction. Development of diastolic dysfunction precedes systolic dysfunction. Subclinical abnormalities of left ventricular function are recognized in both IDDM and NIDDM. More recently, studies using Doppler echocardiography have confirmed abnormal diastolic function, as an early indicator of cardiomyopathy, in asymptomatic patients. These abnormalities correlate strongly with the duration of diabetes and the extent of micro vascular complications. Thanikachalam and associates have reported on the prevalence of subclinical diabetic cardiomyopathy. It was shown that in some cases Cardiomyopathy may be reversible after good control of diabetes.

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