

At one time diabetes mellitus (DM) was considered as a major coronary risk factor along with smoking, hypertension and hypercholesterolemia. But the association of diabetes mellitus with coronary heart disease became so intimate that it is now being considered as the coronary equivalent. Once somebody develops diabetes he always carries the extra risk of various cardiovascular events. The CV risks might be in the –

- Blood vessels in heart causing ischaemic heart disease,
- Renal vessels causing nephropathy,
- Blood vessels in the eye (retinopathy),
- Blood vessels in the brain causing stroke.
- Peripheral arteries causing Peripheral vascular disease.

Excluding the involvement of major blood vessels in the heart microvascular involvement and involvement of the myocardial cells does occur; leading to systolic and diastolic heart failure. These later manifestations come under diabetic cardiomyopathy.

Though the major problem in diabetes is hyperglycemia and the vascular damage is primarily mediated by hyperglycemia but many other factors do play a role. Even similar vascular damage do occur in those who have not yet developed diabetes mellitus; like the metabolic syndrome and prediabetic states (IGT and IFG).<sup>1</sup>

### WHAT HAPPENS?

There occur changes in the large blood vessels, in small blood vessels, at the cellular level and at molecular levels.

### MACROVASCULAR FACTORS

The main problem in the major blood vessels is atherosclerosis. Pathogenesis of atherosclerosis is same everywhere, but certain extra factors in DM operate so that atherosclerosis develops earlier and progresses faster. 97% of the diabetics have dyslipidemia.<sup>2</sup> The lipid abnormality in diabetics is low HDL and high triglycerides. The LDL in these patients is small and dense, which helps them to enter into the endothelial cells more easily and forms stronger attachments with the arterial wall. Small LDL particles are more susceptible to oxidation. Once the LDL particles get oxidized they become immunogenic and attracts immune cells and initiates the process of inflammation. During the process various factors are released which helps atherogenesis. There occurs migration of smooth muscle cells, proliferation of endothelial cells and accumulation of leucocytes. LDL particles get glycated which increases its half life and it remains longer in the circulation and in the atheromatous plaque. At the same time glycation of

HDL shortens its life span; there by reduces its beneficial effects. High triglyceride (often an essential component of diabetes or metabolic syndrome) level helps in production of small LDL and decreased HDL transport to liver encouraging high level of LDL and promoting the atherosclerotic process.<sup>3</sup>

Endothelial dysfunction also exists in diabetics. The net result of endothelial dysfunction is vasoconstriction which also contributes to atherosclerosis. Thus the lipid abnormality and the endothelial dysfunction are responsible for the macrovascular changes in diabetics and its consequences.

### MICROVASCULAR FACTORS

Usually we mean retinopathy, nephropathy and neuropathy as the microvascular complications in diabetes mellitus, but such changes do occur all over the body. This small vessel disease is not related to atherosclerosis and not related to lipid abnormality. At physiological level microcirculation is maintained by local autonomic nerve supply and substances released by endothelium and metabolites released locally. Capillary permeability to different metabolites and the intactness of the junction between the endothelial cells are the most important factors in this regard. Normally the endothelium produces enough nitric oxide (NO) which acts as strong vasodilator. In diabetes all these undergo changes. Due to autonomic neuropathy local autoregulation of blood flow is not maintained. The thickness of the capillary basement membrane increases leading to inadequate exchange of materials (metabolic products and nutrients) between blood and tissues. Often this gives a sense of fatigue on exertion. However the junction between the endothelial cells becomes less efficient. There is alteration in charges at these points. This causes leakage of macromolecules like albumin. Hence micro-albuminuria is considered as the evidence of microangiopathy in DM.<sup>4</sup> There is decreased release of NO and increased secretion of endothelin-1 which is a vasoconstrictor substance. The result is diffuse vasoconstriction almost in all the tissues leading loss of their vitality. These chemical changes have been noticed in both in DM as well as in metabolic syndrome. Decreased NO production is related to insulin deficiency and insulin resistance.

One of the consequences of microvascular complication due to diabetic autonomic neuropathy (DAN) is sudden cardiac death and higher overall cardiac death.

### CELLULAR FACTORS

The cells that are involved in vascular damage are inflammatory cells and the adipocytes. It has been observed by researchers that diabetes mellitus is a chronic

low grade inflammatory disorder.<sup>5</sup> The inflammation is mostly confined to the vascular endothelium. The leucocytes involved in the inflammation release a lot of mediators and themselves are under influence of several chemicals like cytokines and chemokines. The inflammation precedes much before frank diabetes mellitus; even prediabetic states. This inflammatory process is both responsible for the vascular damage as well as progression of diabetes mellitus. Hence this is the common source of both the processes. The effect of inflammation is decreased production of NO and increased production endothelin-1. The inflammatory mediators released cause enhanced capillary permeability, apoptosis and generation of reactive oxygen species. Certain workers have detected rise in sialic acid level persistently in majority of Type-2 diabetics.<sup>6</sup>

Adipocytes in diabetics are extremely active. They release different types of adipokines (Tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , interleukin-6, plasminogen activator inhibitor-1).<sup>7</sup> These are all proinflammatory markers. Level of all these increases as obesity increases. Adiponectin which is an anti-inflammatory marker is found to be reduced in obese individuals; hence contributing to the damaging effects of inflammatory markers. These changes are observed both in diabetics and prediabetics.

### MOLECULAR FACTORS

Several molecules are involved in the process of vascular damage in diabetes mellitus. Of them the most important are the reactive oxygen species (ROS). These act as free radicals. Free radicals are molecules having unpaired electron in their outermost orbit. This makes them highly reactive. They are primarily released from mitochondria during the process of oxidative phosphorylation.<sup>8</sup> They are also released during the process of inflammation by the leucocytes. This has been observed both in animal experiments and in studies in human. These reactive species react with various cell organelles as well as cell membrane causing damage to them. Free radicals in excess are also generated due to metabolism of glucose and free fatty acid in hyperglycemic states of DM. This exceeds the capacity of the cells to tackle the extra free radicals and thereby cell damage occurs. At molecular level there are four basic mechanism by which diabetes mellitus brings tissue damage. These are:

- Activation of the polyol pathway
- Increased production of advanced glycosylation end products
- Activation of protein kinase C
- Activation of hexosamine pathway.

All these four mechanisms are initiated and propelled by ROS released by mitochondria. Hence oxidative stress is the important mechanism of diabetic organ damage.

### OTHER FACTORS

The major vascular events in diabetics is thrombosis; either giving rise to myocardial infarction, cerebral infarction or blockage of peripheral arteries. Hence the final step is thrombosis. Here the platelet and the coagulation factors finish the total process of vascular damage. Changes

in them produce a state of hypercoagulability.<sup>9</sup> It has been observed that platelet aggregation and adhesion is increased in DM. Activation of platelets releases so many factors like beta-thromboglobulin, platelet factor-4, thromboxane-B<sub>2</sub>. In some patients the platelet is so much activated that use of aspirin is not effective in these patients. This has been attributed as aspirin resistance. Similarly coagulation markers are also found to be elevated. Prothrombin activation fragments, thrombin anti-thrombin complexes are found to be elevated in diabetics. Some workers have also detected high level of fibrinogen, factor-VII, factor-VIII, Factor-XII, kallikrein and von Willebrand factor. It is also noticed that the fibrinolytic activity is reduced. This also encourages thrombotic process.

In addition to the vascular changes causing several CV events, the myocardium is also directly damaged in diabetics. These patients present as heart failure. Both systolic and diastolic heart failure has been observed in the absence of any vascular events.<sup>10</sup> It has been seen that for rise of Hb A<sub>1c</sub> by 1% there is 12% rise in heart failure in diabetic population. The factors that lead to heart failure, particularly diastolic heart failure are micro vascular disease, myocardial fibrosis, myocardial hypertrophy, DAN and failure of release of NO.

### SUMMARY

The cardiovascular damage in diabetes mellitus is multifactorial. The process starts well before frank hyperglycemia develops either as prediabetic stage or metabolic syndrome. It is always better to remain free from these states by regular exercise and not developing obesity. CV changes are so vividly associated with DM that it deserves to be mentioned as CV risk equivalent.

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