INTRODUCTION:

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and the health care system.

Macrovascular disease (MVD) is the most prevalent complication amongst diabetics in the west. Almost 2/3rd of deaths in diabetics is due to coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral vascular disease (PVD). The situation has worsened in the post insulin era due to control over acute complications and infections in diabetics. The problem although more marked with Type-2 diabetics is also a major cause of morbidity and mortality in Type-1 diabetics, therefore the American Heart Association has designated Diabetes Mellitus (DM) as a major risk factor for cardiovascular disease.

As far as other complications are concerned, in the U.S., DM is the leading cause of End-stage renal disease (ESRD), non-traumatic lowerlimb amputation and adult blindness. Chronic Hyperglycemia per se is the major risk factor for initiating chronic inflammatory response in subjects with DM. Inflammatory response involving multiple mediators such as C-reactive protein (CRP), cytokines like Tumor necrosis factor alpha (TNF – α) and Interleukin - 6 is well appreciated in subjects with diabetes.

BURDEN OF MVD IN DIABETICS WITH SPECIAL REFERENCE TO INDIANS:

Atherosclerosis (AS) is more prevalent in subjects with DM and quantum of involvement of vascular channels is more profound as compared to non diabetics. Such association suggested the role of chronic hyperglycaemia to be the common determinant as most other genetic, hormonal and metabolic parameters, thought to be risk factors (RF) or determinants for arteriosclerosis (AS), are dissimilar in these two protein types DM. Prospective study and retrospective analysis in families with Type 2 diabetics had revealed that MVD foreruns the overt development of chronic hyperglycemia by decades, suggesting a likelihood of AS and DM sharing a "common soil" for growth and development in the individual.

Studies from USA and other western countries had shown that CAD, acute myocardial infarction, congestive heart failure and PVD are the commonest morbidities associated with DM. The situation in Indians is different as compared to the west because the four major risk factors for CAD viz hypercholesterolemia, hypertension, DM and cigarette smoking are not very prominent among Indians with CAD as compared to the Framingham cohorts. However, MVD is one of the most established complications in diabetics in India and further there is steady rise in the incidence of CAD amongst the urban population as well as amongst diabetics (Table-1 and Table-2). The prevalence of PVD is much less amongst Indians as compared to diabetics from the west (Table-3). Although there has been substantial increase in the prevalence of PVD in Indians where it varies from 0.8% in epidemiological study to 10% in hospital based publications, it is substantially low as compared to data published from Germany, Greece, USA, UK. Where almost 80 – 90% of foot lesions in diabetics is due to Atherosclerosis.

The prevalence of CVD varies from 3.4 to 9.2% amongst diabetics in India. However the prevalence of DM amongst patient with CVD is much higher as compared to CAD or PVD (Table-5). Further DM is more common (22.1%) a cause for cerebral infarction then cerebral haemorrhage (6.35%) as shown by studies from India.

DISTRIBUTION AND PROFILE OF AS IN DIABETICS VERSUS NON-DIABETICS:

Atherosclerosis tends to occur in patches with predilection for particular regions in the vascular channels. In the coronary circulation the proximal left anterior descending artery (LAD), the carotid artery at the bifurcation in case of cerebral circulation and abdominal aorta at the origin of renal arteries are more susceptible to develop AS than the other parts of arterial tree. The growth of AS plaques does not occur in smooth linear pattern, but rather discontinuously with periods of waxing and waning of the
The process of AS is more widespread and extensive with rapid progress in patients with DM as compared to non-diabetics. Beside co-existence of the other three risk factors (RF) like dyslipidemia, hypertension and smoking can increase the prevalence of AS in a multiple progressive manner. Studies on coronary angiography had shown higher prevalence of multi-vessel disease along with more extensive involvement in Indian diabetics as compared non-diabetic cohort. Further studies from South India had shown that at any given age diabetic subjects had higher values of intima-media thickness than nondiabetics where the difference reached statistical significance after the age of 50 years. All these factors contributed to accelerated and extensive AS in Indian study with DM with hyper prevalence for coronary and cerebral circulation.

THE BIOCHEMICAL MECHANISMS CONSEQUENT TO METABOLITES OF GLUCOSE CAN BE SUMMARIZED AS:

a. increase in non-enzymatic glycosylation (glycation) of proteins with advanced glycatend end products (AGE),

b. activation of polyol pathway,

c. activation of DAG-PKC cascade

d. oxidative stress.

AND

e. Insulin resistance and hyperinsulinemia

HYPERGLYCAEMIA

The contribution of hyperglycemia as an independent determinant or RF for developing MVD, coronary artery disease (CAD) in particular, has become obvious from the United Kingdom Prospective Diabetes (UKPD) study. Several biochemical mechanisms consequent to metabolites of glucose can affect numerous cellular pathways both intra and extracellularly, that can have adverse effect on the vascular cell walls. These mechanisms can be summarized as:

a. Increase in non-enzymatic glycation of proteins. Besides excess glycation of intracellular proteins and plasma membranes; glucose forms glycatend compounds or oxidants by causing glycation of primary amines of amino acids in extracellular matrix and fluid. These glycatend products can act on inflammatory cells to release cytokines or directly act on vascular cells and cause vascular dysfunction. The ketoamine can undergo further modification and degradation to form insoluble complexes referred to as advanced glycatend end products (AGE). Collagen, present all over to body, are rich in lysine, have long biological half life and thus most susceptible to glycatend and AGE formation. Such changes in the collage of the vascular wall lead to excess LDL trapping and oxidation. Interestingly there is a threshold for these glycatend affect in patients with DM i.e. there is correlation between the degree of glycemia and MVD, whereas among people without DM there is no such correlation as they fall below the glycemic threshold.

b. Activation of polyol pathway. Excess amount of glucose enters the intracellular compartment with the help of glucose transporters GLUT-1 and also GLUT-4 and get metabolised through the sorbitol pathway. On conversion to excess of sorbitol they cause change in the redox potential or alter signal transduction pathways viz. activation of DAG and PKC. All these process adversely affect permeability, contractility, extracellular matrix, cell growth, angiogenesis, cytokine action and leukocyte adhesions in vascular cells. It enhances injury to vascular endothelium and propagates both microvascular and macrovascular complications.

Injury to endothelium cause release of arachidonic acid and prostaglandin E2, enhanced sodium/potassium ATPase activity and so cellular activity. Besides, there is increased expression of Transforming Growth Factor β (TGF-β), TypeIV and Type VI collagen, fibronectin which suppress proteoglycans in the extracellular matrix. Increase of flux of glucose via hexosamine formation leads to free radical generation and auto oxidants. Changes in the redox potential also adversely affects impulse transmission and functional activity in neuronal tissue.

c. Activation of diacylglycerol (DAG) protein kinase C (PKC) cascade. Intracellular DAG is the physiological activator of PKC. DAG is derived from multiple sources including hydrolysis of phosphatidylinositol, metabolism of phosphatidylcholine or de novo synthesis. The PKC consists of a family of 11 isomers representing the major targets for lipid second messengers. Persistent hyperglycemia causes rise in DAG-PKC levels intracellularly in many tissues including aorta, heart, retina, glomeruli and even insulin sensitive tissues like liver and skeletal muscle but not in brain or peripheral nerves. However, transient rise in blood glucose does not cause this and such increase in intracellular DAG-PKC may require 3 to 5 days of persistent hyperglycaemia. Increased activation of DAG-PKC cascade leads to multiple cellular and functional abnormalities in vascular cells. There occurs increased release of arachidonic acid and prostaglandin E2 production vis-a-vis decreased Na+, K+ ATPase activity which in turn affects cellular integrity as well as function like contractility, growth and differentiation. PKC activation can increase expression of transforming growth factor Beta (TGF-Beta) which increases Type IV and Type VI collagens and fibronectins which suppress proteoglycans in extracellular matrix. Less production of proteoglycans like glucosaminoglycans in capillary endothelial surface leads to defect in lipoprotein lipase (LPL) binding and consequent poor clearance of VLDL. These metabolic defects lead to the typical dyslipidemia of DM (discussed below). Further, increase in collagen, particularly Type-IV, leads to expansion of the basement membrane with vascular dysfunction.
Insulin in physiological levels has antiatherogenic actions

d. Increase of flux via the hexosamine metabolism. Non-enzymatic glycation is a process that affects protein at any situation whether structural protein, coagulation protein, lipoprotein or carrier proteins in circulation. Hyperglycaemia is an important source of oxygen free radicals (OFr) production and contributes to glucose auto oxidants and increased AGE formation. All these combinedly increased the oxidative stress in the diabetic individual. The oxidative stress (manifests as increase in NADH/NAD ratio in various cells and tissue with less of nitric oxide (NO) production in vessel wall. The biological activity of such cells and tissue are altered. In the vascular channel the effect can be depressed activity of LPL, decreased insulin action with increased peripheral resistance, attenuated fibrinolysis, increased production of von Willebrand factor (vWF) and endothelin, defective production of endothelial derived relaxation factor (EDRF) and increase in oxidised LDL. Oxidation, which is enhanced in diabetic state, not only modifies the phospholipid content of LDL but also the aminoacid side chains of Apoprotein B100 (Apo B100). Such oxidized ApoB100 mediates excess of receptor uptake of LDL by endothelial cell while the oxidized LDL per se is:

i. More recognized by macrophage scavenger receptors and readily taken up by foam cells - fat laden scavenger cells / smooth muscle cells (SMC) in atheromatous lesions. Once taken up by foam cells the degradation of oxidized LDL is impaired leading to further accumulation of lipids m these cells.

ii. Oxidised LDL increases the adhesion of circulating monocytes to damaged endothelium, enhancing their migration into the vascular intima.

iii. Oxidised LDL is more immunogenic forming antibody-lipoprotein complex which stimulate foam-cell formation and platelet aggregation as compared to non-oxidised LDL.

iv. Oxidised LDL has an increased affinity for getting bound to glucose mediated croslink present in the matrix of the vascular intima. These are various hitherto known mechanisms by which increased oxidative stress can lead to enhanced AS and MVD in DM.

The enhanced flux of glucose into the cells via hexamine formation has been discussed above under (c) and (d). In general the Na+, K+ pump is defective in diabetic subjects with uncontrolled hyperglycaemia. This allows the excess flux and the likely explanation is through DAG-PKC activation.

e. Hyperinsulinemia –Insulin Resistance

Insulin in physiological levels has antiatherogenic actions whereas in insulin resistant (IR) or hyperinsulinaemic (HI) situations it causes attenuation of AS. At physiological levels as insulin increases NO production, retards migration and growth of SMC from the subendothelial layer of vascular wall. The vascular cells are capable of responding to insulin with a wide variety of action. Insulin in situation of HI exerts its adverse effects on the vessel wall through other mediators and mechanisms rather than having a direct effect like enhancing mitogenicity.

In conditions of HI/IR as seen in obese Type 2 diabetics, insulin may lose its metabolic effect but retains its growth stimulating effect on vascular wall cells. In patients with HI, insulin exerts its atherogenic effect on SMC by enhancing the mitogenic action of more potential growth factors like platelet derived growth factor (PDGF) and insulin like growth factor (IGF). IR and HI can trigger various coagulation abnormalities that act as important factors for development of MVD in diabetics -more so with Type 2 diabetics. Generation of NO is suppressed in patients with HI. In brief the mechanisms are:

I. Insulin, proinsulin and oxidized LDL can induce increased expression and secretion of (plasminogen activator inhibitor-l (PAI-l) by endothelial cell lines and hepatocytes. As PAI-l is a fast acting inhibitor of fibrinolysis it helps in thrombogenesis and vascular occlusion. PAI-l is now considered as apart of insulin resistance syndrome (IRS).

II. Concentrations of endothelial cell protein, vWF are elevated in IRS. This is a marker of endothelial cell dysfunction/ damage and raised levels in plasma suggest endothelial cell injury and activation of atherogenesis. Further, secretion of vWF and other procoagulants as well as adhesive molecules indicate the existing procoagulant state.

III. Levels of fibrinogen are elevated in IRS. This being an acute phase protein synthesized by liver in response to circulating interleukin-6 (IL-6) suggest role of acute phase cytokines in the abnormalities of coagulation and endothelial function. This is more so in obese diabetics where the adipose tissue secretes IL-6 and adipose tissue-expressed tumour necrosis factor-alpha (TNF-alpha) -both are proinflammatory cytokines and enhance atherogenesis.

Evidences from studies published in 1979 and 1980 from various parts of Europe and Australia had shown that HI is a predictor of future development. AS in men while the Atherosclerosis Risk in Communities (ARIC) study revealed the reverse phenomenon i.e. HI was RF for MVD in women. There were reports suggesting that HI did not “correlate with AS in non-caucasians. Moreover, the major controversy was raised regarding the” estimation of insulin in plasma since most assays also estimated proinsulin along with insulin. It was then thought that the proinsulin was the main culprit for increased prevalence of MVD in Type 2 DM with HI and such HI was spurious due to non-specific assay.

However, two prospective studies, the Quebec Cardiovascular Study and the British Regional Heart Study that used specific immunoassay for insulin have revealed that, there is a threshold
for the MVD enhancing effect of insulin and an increase of one standard deviation in specific insulin levels conferred a 70 percent increase in cardiovascular risk.

**ADVERSE EFFECT ON LIPID PROFILE**

Dyslipidemia is one of the well known determinants of MVD.

Current knowledge from the West reveals that the major abnormality in diabetics is hypertriglyceridemia with level of cholesterol and LDL being nearly similar to that found in the general population. Hypertriglyceridemia is one of the main markers of IR, even in diabetics selected to be lean or low bodyweight. It is needless to reemphasise today that most studies have endorsed the view that hypertriglyceridemia confers an increased risk for MVD, CAD in particular, in the general population. This risk of TG is independent of HDL. Hypertriglyceridemia refers to a situation of increased TG-rich lipoproteins. On ultra centrifugation of plasma from such diabetics, it will be found that three fourth of TG-rich lipoprotein molecules are smaller dense particles and float at a density range of 12 to 60 Sf. All these particles contain one molecule of ApoB100 and so called intermediate density lipoprotein (IDL). The small dense IDL level is positively correlated with MVD in men with or without DM and is independent of LDL and HDL. Raised TG levels are also associated with increased levels of PAI-1.13

Prospective studies have shown that hypertriglyceridemia may antedate development of MVD in Type 2 diabetics. Plethora of recent data on insulin sensitivity and CAD suggest that there could be a genetic predisposition for hypertriglyceridemia in patients with Type 2 DM. Such genetic abnormality is not monogenic in origin and appears to the determined by genes that cluster in a particular region of one chromosome so as to express concurrently and produce the complex situation of hypertriglyceridemia in Type 2 diabetics with increased propensity for MVD. Mutations have been detected in LPL gene locus present in chromosome 8 which can produce impaired clearance of VLDL from circulation. The apoproteins AI, C III and A IV are known to modulate TG transport and metabolism where AI and A IV stimulate while C III suppresses LPL activity. The genes for these apoproteins have been found to be located on the long arm of Chromosome 11 and at least 14 mutations have been detected in patients with Type 2 DM. These mutations can produce apoproteins and LPL that are defective in function and so slow VLDL clearance with consequent persistent hypertriglyceridemia.13

The near normal levels of plasma cholesterol in diabetics may be, in reality misleading since at any given concentration of cholesterol, diabetics are two to four times more prone to develop CAD as compared to non-diabetics. This could be due to the reason that, the mere quantitative value of cholesterol or LDL may not be important as LDL may be modified viz. nonenzymatically glycated, undergone oxidation, changed sized to smaller or dense particles. Over and above their interaction with coexistant no-lipid RIs like AGE, hypertension, changes in the coagulation cascade etc. make them more atherogenic in diabetics.

**ADVERSE EFFECTS ON RHEOLOGY:**

As already discussed increased PAI-I, vWF and fibrinogen can enhance vascular complications. Level of factor VII and VIII are elevated along with thrombin, anti-thrombin complexes, while anti-thrombin III, protein C and S are reduced. Platelet abnormalities are also observed in both type- I and type-2 DM leading to increased aggregation and adhesion which make the subjects more prone for both micro and macrovascular complications.

**SUMMARY**

Therefore chronic hyperglycemia is the common determinant, as most other genetic, hormonal and metabolic parameters thought to be risk factors or determinants for arteriosclerosis are profoundly influenced by persistent rise in blood glucose levels in patients with DM.

Enough scientific evidence have flooded the literature to justify the role of hyperglycemia as the common mechanism behind both micro and macrovascular complications.

Similarly, knowledge gathered from outstanding prospective studies like D.C.C.T. in subjects with I.D.D.M. (Type 1) and U.K.P.D.S. in N.I.D.D.M. (Type 2) have revealed that tight control of blood glucose level is the bottom line for prevention of complications in diabetic subjects.

**REFERENCES**


