PREVENTION OF DIABETIC COMPLICATIONS: IS IT POSSIBLE?

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INTRODUCTION
Diabetes Mellitus (DM) is a metabolic disorder of continuum. Its onset can be prevented if it is possible to predict its occurrence. A positive family history, presence of islet cells antibodies; genetic predictors help us in doing so in a reasonably good number of high risk patients.

With ever increasing incidence of DM it has become one of the major global and health problems. Presently its prevalence has been reported as 13-15% in urban areas of India. Some workers believe that, equal number of undiagnosed diabetics are present in India, while others have reported nearly 12% yearly increase diagnosed diabetics in our country(1).

The World Health Organisation (WHO) estimates that by 2025, worldwide there will be 300 million Diabetics (5.4%). India by then will be a home to more than 57 million Diabetics. This will be the largest number compared to other countries world over. Presently Diabetic population in India is estimated to be approximately 32 million.2

PRIMARY PREVENTION;3-6
Primary prevention aims at identifying persons with risk of developing DM, so that the complications of DM can be prevented. With regards to developing Type 2DM there are many modifiable risk factors viz. overweight, corpulence, consumption of high calorie diet, fried foods, carbonated drinks, smoking, alcohol and lack of physical activity. These risk factors can be changed to active daily routine with healthy food habits i.e. lifestyle modification. The non-modifiable risk factors like ethnicity, race of origin, genetic built and family history of DM, hypertension, coronary artery disease (CAD) and dyslipidemias can be partly neutralized by determined attempts of lifestyle modification and where necessary usage of drugs like metformin, α glucosidase inhibitors and lipid lowering medications.4

Type 2 DM is preceded by a period of IGT and/ or IFG therefore, lifestyle modifications as well as use of pharmacologic agents can prevent or delay the onset of frank DM. The Diabetes Prevention Program (DPP) demonstrated that intensive changes in lifestyle (diet and exercise for 30 min/day five times/week) in individual with IGT prevented or delayed the development of Type 2 DM by 58%. This effect was seen in individuals regardless of age, sex, or ethnic group. In the same study metformin prevented or delayed diabetes by 31% as compared to placebo. The lifestyle intervention group lost 5-7% of their body weight during 3 years of study. Individuals with strong family history of Type2 DM and individuals with IFG or IGT should be strongly encouraged to maintain a normal body mass index (BMI) and engage in regular physical activity. It concluded that metformin, but no other medications ,could be considered in individuals with both IFG and IGT who are at very high risk of progression to diabetes (age <60 years, BMI ≥ 35kg/m²,family history of diabetes in first-degree relatives, elevated triglycerides, reduced HDL, hypertension, or HbA1C>6.0%).6

SECONDARY PREVENTION3-4
Prevention of development of complications in a subject with DM is termed as Secondary Prevention. This involves early diagnosis of DM by regular screening of high risk subjects, institution of healthy habits, regulating diet intake, aerobic exercise, maintaining body weight and tackling insulin resistance if present. Life style changes are relevant especially in Type2 DM patients. Tight glycemic control, correction of lipid abnormalities and maintaining normotensive blood pressure
levels with salt restriction and medication delays the disease process and achieves the objective of secondary prevention. The risk of complication increases as a function of duration of hyperglycemia. Chronic hyperglycemia per se is a 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 (TNF-α) and interleukin-6.

Chronic Complication of DM affects many organ systems and responsible for majority of morbidity and mortality associated with the disease. Chronic complication can be divided into vascular and non-vascular complication. The vascular complication of DM is further divided into micro vascular and macro vascular complication. Non-vascular complication includes Gastroparesis, Infection and Skin changes.

**CHRONIC COMPLICATION OF DM:**

**Micro Vascular**

**Eye disease:** Retinopathy (Nonproliferative/ proliferative), Macular Edema

**Neuropathy:** Sensory and Motor (mono and polyneuropathy), Autonomic

**Nephropathy**

**Macro vascular:**

Coronary artery disease
Peripheral arterial disease
Cerebro vascular disease

**Others**

Gastrointestinal (Gastroparesis, Diarrhoea)
Genitourinary (Uropathy/ sexual dysfunction)
Dermatological complications
Infection
Cataract
Glaucoma

Periodontal Disease

**MECHANISM OF COMPLICATIONS**

Hyperglycemia is an independent determinant or risk factor for developing macrovascular disease, coronary artery disease etc. Several biochemical mechanisms consequent to metabolites of glucose can affect numerous cellular pathways both extra and intracellularly that can have adverse effect on vascular walls. The mechanisms are summarised below-

a. Hyperglycemia leads to formation of advanced glycosylation end products (AGE) via the non-enzymatic glycosylation of intra and extra-cellular proteins. Non-enzymatic glycosylation results from interaction of glucose with amino group proteins. These glycosylated products can act on inflammatory cells to release cytokines or directly act on vascular cells and cause vascular dysfunctions. Collagen present all over the body are rich in lysine and have long biological half life, thus are more susceptible to glycosylation. Such changes in collagen of vascular wall lead to excess of LDL trapping and oxidation. The serum level of AGEs correlates with level of glycemia.

b. Increased metabolism of glucose via sorbitol pathways, on conversion to excess of sorbitol, cause change in redox potential or altered signal transduction pathway via activation of DAG and PK-C which increases cellular osmolarity, generates reactive oxygen species and cytokines which adversely affects cell permeability, contractility of extracellular matrix, cell growth and angiogenesis.

c. Hyperglycemia increases formation of DAG leading to activation of Protein kinase C. PKC alters the transcription gene for fibronectin, type IV collagen, contractile to proteins and extracellular matrix proteins in endothelial cells and neurones. PKC activation can increase in expression of TGF-beta which increases type IV and type V collagen and fibronectin which suppress proteoglycan in extracellular matrix. Less production of proteoglycans like glucosamine in capillary endothelium leads to defect in lipoprotein binding lipase (LPL) binding and consequent poor clearance of VLDL. These metabolic defects lead to typical dyslipidemia of DM. Further increase in collagen, particularly type IV leads to expression of basement membranes with vascular dysfunction.

d. Hyperglycemia increases the flux through hexosamine pathway, which generates fructose -6-phosphate and a substrate for –O- linked glycosylation and proteoglycan formation. Oxygen free radicals increase the oxidative stress which increases NADH/NAD ratio in various cells and tissue with less Nitric Oxide (NO) production in vessel wall.

**HYPERTENSION**

The major cause of mortality with patients with diabetes is cardiovascular disease (CVD). The risk factors of CVD that cluster in subjects with DM include, hypertension, central obesity, dyslipidemia, microalbuminuria, coagulation abnormalities, loss of nocturnal dipping of blood pressure and pulse and LVH. Among the risk factors, hypertension is associated twice more frequently in patients with DM as those without diabetes and accounts for 85% of CVD risk. Association between hypertension and insulin resistance and resultant hyperinsulinemia is well established. In untreated patients with essential hypertension, fasting and postprandial insulin were higher than in normotensive patients regardless of the BMI. Patients with DM have a loss of nocturnal dipping.
of blood pressure (BP) as demonstrated by 24 hr ambulatory monitoring of BP. This is particularly important since loss of nocturnal dipping conveys excess risk of stroke and myocardial infarction.

**MICROALBUMINURIA**

In subjects with Type 2 DM, microalbuminuria is associated with insulin resistance and is a marker of endothelial dysfunction. Elevated systolic BP is a significant determining factor in progression of microalbuminuria. Indeed, there is increasing evidence that microalbuminuria is an integral component of the metabolic syndrome associated with hypertension. Aggressive blood pressure lowering often requiring several drugs is very important in controlling the progressive diabetic renal disease. Target BP recommended by ADA and JNC-VII is <130/80 mmHg.

**DYSLIPIDEMIA**

The most common pattern of dyslipidemia is hypertriglyceridemia and reduced level of HDL. In Type 2 DM there is increase in levels of small dense LDL which are more atherogenic because they are more easily glycated and susceptible to oxidation. Glycated LDLs appear to exhibit altered interaction with endothelial cells, stimulate cytokine production, enhance cholesterol ester synthesis in human macrophages and so enhance the potency for developing accelerated atherosclerosis even at normal LDL levels. An impressive CAD risk reduction in diabetics comes from reduction in blood pressure, lifestyle modification and most importantly by lipid lowering drugs like statins.

ATP-III of the NCEP has established the goal of LDL cholesterol level <100 mg/dl for patients with pre-existing CHD or CHD risk equivalents. NCEP has also determined that an HDL <40 mg/dl and a triglyceride level >150 mg/dl are major risk factors. An optional goal of achieving an LDL-C of less than 70 mg/dl was proposed for very-high risk individuals such as patients with diabetes and known CHD.

**OPHTHALMOLOGICAL COMPLICATIONS OF DIABETES MELLITUS**

There are plethora of epidemiological evidences of association between poor glycemic control and development of diabetic retinopathy (DR). The DCCT report revealed that, at intensive glycemic control in Type 1 patients over 6.5 years caused 76% reduction in the risk of developing retinopathy. In the tight glycemic group compared to the controlled group. The rate of progression of existing retinopathy was slowed by 54% and the risk of developing severe non proliferative or proliferative retinopathy was reduced by 47%. The UKPDS followed up Type 2 DM patients over a 9 year period and showed a 21% reduction in progression of retinopathy, and a 29% reduction in the need for laser therapy in patients with tight glycemic control. The long term benefits of improved glycemic control are therefore clear with regards to developing retinopathy in both Type 1 and Type 2 diabetics.

Other risk factors in addition to chronic hyperglycemia are hypertension, nephropathy and cardiovascular autonomic neuropathy. Elevated systemic blood pressure may be a risk factor for diabetic retinopathy or just an indicator of macrovascular dysfunction and is manifested as microalbuminuria. It leads to complications in kidney as well as eyes.

Wisconsin Epidemiologic Study, during a period of 10 yrs follow up, studied the progression of retinopathy and the development of proliferative retinopathy. Such complications were highest in patients with Type 2 DM on oral agent and diet control. Further, the Wisconsin study revealed that systolic BP was related with onset of non-proliferative DR whereas diastolic BP was associated with its progression.

The improved glycemic control can significantly delay the development of non-proliferative retinopathy and postpone its progression to proliferative retinopathy. DCCT demonstrated that improvinglymicemiccontrolreducednonproliferative and proliferative retinopathy (47% reduction) and intensive diabetes management group would gain 7.7 additional years of vision.

**DIABETIC NEUROPATHY (DN)**

DN occurs in approximately 50% of individuals with long standing Type 1 and Type 2 DM. It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. The development of neuropathy co-relates with the duration of diabetes and glycemic controls. Both myelinated and unmyelinated fibres are lost. The ADA recommends screening for distal symmetric neuropathy as early as the initial diagnosis of DM. Similarly, screening for autonomic neuropathy to be done 5 years after diagnosis of Type 1 DM but at the time of diagnosis of Type 2 DM.

All individuals with diabetes should be screened annually for both forms of neuropathy. Intensive therapy reduces the risk of developing clinical neuropathy in 60% cases.

**DIABETIC NEPHROPATHY**

The natural history of diabetic nephropathy has been generally viewed as a progressive pathway from microalbuminuria to end stage renal disease. Initially there are glomerular hyperperfusion and renal hypertrophy with increased GFR. During first 5 years of DM there is thickening of glomerular basement membrane, glomerular hypertrophy and mesangial volume expression as the GFR reduces to normal, 40% of individuals begin to excrete small amount of albumin in urine. Over 50% of individuals in next 10 years progress to macroalbuminuria. Once macroalbuminuria is present there is steady decline in GFR and 50% individual progress to
ESRD in 7-10 yrs. Once macroalbuminuria develops, blood pressure rises stiffly and the pathologic changes are likely irreversible. The level of glycemia seems to be the strongest factor influencing the onset of microalbuminuria. Strict control on blood pressure should be maintained (BP <130/80 mmHg) in diabetic individuals without proteinuria and blood pressure lower than 125/75 mmHg in those with proteinuria. Administration of ACE inhibitors or ARBs is recommended for regular use to reduce progression from microalbuminuria to macroalbuminuria.

**DIABETES AND CORONARY ARTERY DISEASE**

Cardiovascular disease is increased in individuals with Type 1 or Type 2 DM. Framingham Heart Study revealed a marked rise in PAD, CHF, CHD, MI and sudden death (risk increase from one to fivefold) in patients with DM. The American Heart Association has designated DM as a “CHD equivalent”. Type 2 diabetes patients without a prior MI have similar risk for coronary artery related event as non-diabetic individuals who had a prior MI. The absence of chest pain (silent ischemia) is common in diabetics and a thorough cardiac evaluation should be considered in individual undergoing major surgical procedures. CHD is more likely to involve multiple vessels in individuals with DM. The increase in cardiovascular morbidity and mortality appears to the synergism of hyperglycemia with other cardiovascular risk factor. Type2 DM increases the death rate twofold in men and fourfold in women. Risk factors include dyslipidemia, hypertension, obesity, reduced physical activity and smoking. 

Individual with insulin resistance and DM have elevated level of plasminogen activator inhibitor (PAI-I) and fibrinogen which enhances the coagulation process and impair fibrinolysis, thus favouring thrombosis. Diabetes is also associated with endothelial vascular smooth muscle and platelet dysfunction. ADA has emphasized the importance of glycemic control and cardiovascular risk factor modification in individuals with DM. In both the DCCT (type 1 diabetes) and the UKPDS (type 2 diabetes), cardiovascular events were not reduced by intensive treatment during trial but were reduced at follow up 10 -17 years later (this effect has been termed legacy effect or metabolic memory).

**SUMMARY**

The DCCT, Kumamoto Study, UKPDS study, the ADA and other prospective studies have concluded that, significant and consistent effort of intensive therapy leading to tight glycemic control in subjects with DM reduces risk of development and progression of long term complications. Control of blood glucose level, blood pressure and maintaining desirable lipid profile outweigh their cost in benefiting the subject with DM. The goal of all patients should be to lower blood glucose level to as close to normal range as safety and life style allow. The HbA1C level should translate into lower risk of complication. Thus, complications in subjects with DM can definitely be prevented or at least contained and delayed with the above efforts.

**REFERENCES**