Prevention of Complications of Diabetes

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CHAPTER OUTLINE

INTRODUCTION

Diabetes, a potentially life threatening disorder, is considered as "an apparent epidemic which is strongly related to life style and economic change" by the World Health Organization (WHO).[1] Lifestyle and economic drift along with increase in life expectancy has markedly increased the diabetes epidemic in India by affecting more than 32 million people presently.[2] This metabolic disorder causes profound alterations in both the micro and macro sections of the vascular tree affecting nearly every organ in the body.[3,4] Diabetes magnifies the risk for vascular diseases several fold and is thus one of the major causes of morbidity and mortality worldwide.[5,6] Surprisingly, in spite of the enormous growth in the field of diabetology, measures taken to prevent these dangerous complications of diabetes are woefully inadequate.

Among the several categories of diabetes, the most common is type 2 affecting more than 85% of the total diabetic population, the next common being type 1, accounting for around 5-10% world wide. Although the pathophysiology of type 1 and type 2 diabetes are different, the pathological sequence of complications appears to be similar in both these types of diabetes.[7] Hence they are considered together in this chapter. The micro and macro vascular complications of diabetes are indicated in Figure 1.

PREVALENCE OF MICROVASCULAR COMPLICATIONS IN INDIAN POPULATION

The most specific complications of diabetes are microvascular complications (retinopathy and nephropathy) of which diabetic retinopathy is considered as the hallmark of diabetes. Diabetic retinopathy is the most common cause of blindness in the working age group in developed countries.[8] Prevalence of this disorder among type 2 diabetic subjects in Indians has been reported to range from 7.3%-4.1%.[9-12] Diabetic neuropathy may affect around 50% of all diabetic subjects and is considered to be a main cause for morbidity. Prevalence of peripheral neuropathy in type 2 diabetic subjects has been reported to be 17.5-19.1% in India[13,14], while autonomic neuropathy was prevalent in 35.7%[15]. Diabetic nephropathy is the leading cause of end stage renal disease worldwide[16] and accounts for more than one third of all cases of end stage renal disease. The stage of microalbuminuria, which is reversible, precedes overt proteinuria, which is indicative of definitive or irreversible diabetic nephropathy. The prevalence of microalbumnuria was reported to be 36.3% at a major referral centre in south India.[17]

PREVALENCE OF MACROVASCULAR COMPLICATIONS IN INDIAN POPULATION

Compared to type 1 diabetes, type 2 diabetes has a higher risk for cardiovascular disease, which is

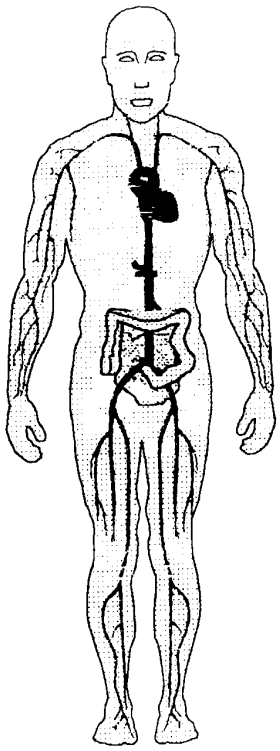

Fig. 1. Diabetes complications

estimated to be 2-4 fold higher compared to non-diabetic subjects.[18] This is because type 2 diabetes is a component of the metabolic cluster, which is associated with other risk factors like insulin resistance, dyslipidemia, hypertension, abdominal obesity and prothrombotic state.[19] Cardiovascular disease includes peripheral vascular disease, cerebrovascular disease and coronary artery disease all of which are atherosclerotic in origin. Prevalence of coronary artery disease is also increasing at an alarming proportion in India. The present prevalence of this disease among Indians ranges from 9%-14%.[20,21] Prevalence of CAD among diabetic subjects is reported to be 17-21%.[20,22] The prevalence of peripheral vascular disease (PVD) is several fold higher in diabetic patients compared to non-diabetic subjects but the prevalence of PVD appears to be relatively lower in Indians.[23] In the Chennai Urban Population Study (CUPS), the prevalence of PVD was 3.2% among non-diabetic subjects while among diabetic subjects, it was 6.3%.[23]

DIABETES COMPLICATIONS-ECONOMIC BURDEN:

Diabetes is an expensive disease.[24-26] Most of the expenses incurred could be attributed to the morbid complications. Treatment of diabetic complications constitutes the highest cost. The expenses include both direct cost of treatment and indirect cost due to man-hours lost in loss of productivity. Medical expenditure for a diabetic is estimated to be two to five times more than a non-diabetic subject.[24] This imposes a heavy burden both at the individual and at the societal level. which underscores the need for prevention of complications of diabetes.

Prevention of Complications:

The natural history of type 2 diabetes provides chances for prevention at three transition points (Figure 2). Primary prevention targets prevention of diabetes itself by early diagnosis through screening programmes, which is ven that presently there are very few drugs targeting the complications directly. Preventive approaches to diabetes complications can be categorized into three levels, first the early approach where early detection and appropriate treatment are the cornerstones for delaying the onset of the diabetic complications. Once some complication sets in, preventing progression of the same would form the second approach or the intermediate approach by introducing specific drugs and life style intervention for combating complications. Third would be the late approach where complications have reached a very critical stage and interventional procedures like surgery are required to ameliorate progression to end stages of the complications (Figure 3).

Early detection of diabetes complications (Screening)

Early detection of diabetes complications by routine screening is an important aspect in prevention of diabetes complications. Screening is beneficial in diseases, which impose a significant burden on the society, where the natural history is known and intervention in early stages can prevent further progression of the disease. Diabetes satisfies all these criteria. Several studies have clearly demonstrated that intervention at an early stage can help in preventing morbidity and mortality.[27-31] The American Diabetes Association (ADA) in its clinical practice recommendations[32] has indicated the frequency of screening for various complications of diabetes.

Diabetic retinopathy: Even if visual symptoms are absent, initial retinal screening is recommended at the time of diagnosis for type 2 diabetic subjects and

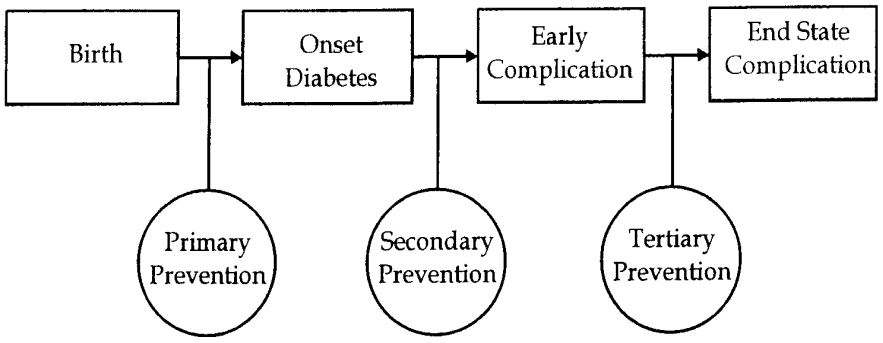

Fig. 2. Stages of prevention of diabetes

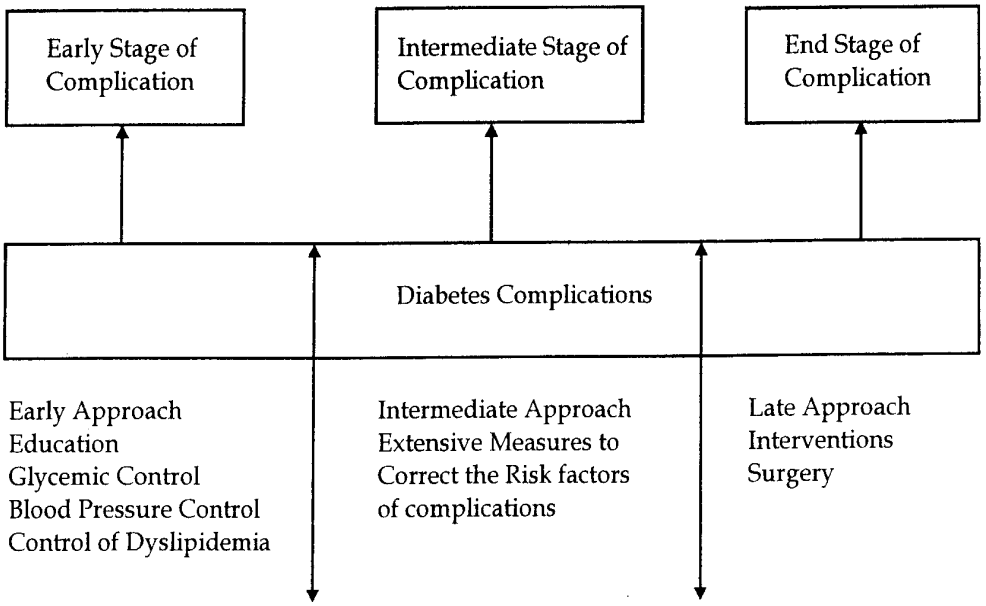

Fig. 3. Strategies to protect target organ damage in diabetic subjects

for type 1 diabetic subjects, within 3-5 years after diagnosis of diabetes when patiens is age 10 years or older. Thereafter, an annual screening is recommended for all diabetic subjects regardless of the type of diabetes (Table 1). Since retinal screening involves pupil dilatation, a detailed eye examination by an ophthalmologist is advisable. In patients with any degree of retinopathy, more frequent examinations are indicated. In diabetes complicating pregnancy a comprehensive eye examination at the first trimester and a close follow up throughout pregnancy is recommended by the ADA.[32] Retinal colour photography helps to document early retinal lesions while Fundus Fluorescein Angiography (FFA) helps to document diabetic macular edema and subtle new vessels in the retina.

Diabetic nephropathy: In the natural history of diabetic nephropathy, excretion of low but abnormal levels of albumin in the urine is considered as the initial stage and is referred as microalbuminuria which is also regarded as incipient nephropathy. Detection at this stage is helpful, as sufficient evidence has accumulated to show that intervention at this stage prevents progression of the disease and indeed sometimes even reverses to normoalbuminuria stage.[33-35] In addition to hyperglycemia, hypertension is also a contributing factor for diabetic nephropathy which could also be controlled using asdequate measures. Thus detection of microalbuminuria in diabetic subjects is crucial to prevention of overt diabetic nephropathy. According

Table 1. Screening schedule for diabetic complications

Complications	Test to be done	First screening – When ?	Monitoring
Macrovascular complications			
Peripheral vascular disease	Examine pedal pulses, auscultate for bruits Peripheral doppler – ankle brachial index	At diagnosis for type 2 diabetes ; As clinically appropriate for type 1 diabetes At diagnosis for type 2 diabetes	Annually
Coronary artery disease	12 lead electrocardiography	As clinically appropriate for type 1 diabetes	Annually
Microvascular complications			
Diabetic retinopathy	Retinal screening – Ophthalmoscopy / fundal photography Visual acuity	At diagnosis for type 2 diabetes 3-5 years after diagnosis for type 1 diabetes	Annually
Diabetic nephropathy	Microalbumniuria – spot urine type 1 diabetes	At diagnosis for type 2 diabetes 3-5 years after diagnosis for	Annually
Peripheral neuropathy	Foot examination Assess protective sensation in feet (Semmens-weinstein 10G monofilament) Biothesiometry Plantar pressure measurement	At diagnosis for type 2 diabetes As clinically appropriate for type 1 diabetes	Annually

to the ADA clinical practice recommendations, annual screening of microalbumnuria is recommended in type 1 and type 2 diabetic subjects (Table 1). The easiest method as suggested by ADA for diagnosis of microalbuminuria is measurement of the albumin to creatinine ratio [ACR] in a random spot collection. Microalbuminuria is diagnosed if ACR is ^{3}30mg/ mg of creatinine while ACR ^{3} 300mg/mg of creatinine is categorized as clinical albuminuria. Care should be taken while diagnosing microalbuminuria because conditions like exercise, urinary tract infection, marked hypertension, heart failure and acute febrile illness can cause a transient increase in excretion of albumin in the urine. As day-to-day variability has been observed in albumin excretion, at least two to three collection within a time span of 3 to 6 months is required for diagnosis of microalbumniuria.

Diabetic neuropathy: Though neuropathic pain is one of the important causes of morbidity in diabetic subjects[36], unlike microalbumniuria there is no direct measure for screening of peripheral neuropathy. Several tests may be necessarid to designate a subject as having diabetic neuropathy. To determine the small fibrue function, protective sensation in the feet, temperature discrimination threshold and skin integrity tests could be used. For large myelinated fibrues, vibration perception threshold [VPT] using biothesiometry has been shown to be a good predictor of foot ulceration.[37] Though not used for routine purposes, motor and sensory conduction velocities gives an assessment of function of large myelinated fibres. Wasting, weakness and ankle reflexes would indicate alterations in motor nerve function. For detecting sensory nerve dysfunction, vibration using tuning fork, sensitiveness to monofilament and pin-

prick should be useful. Annual screening for peripheral neuropathy is recommended using measures suggested in Table 1.

Macrovascular disease: A common cause of foot amputations in diabetic subjects is peripheral vascular disease [PVD]. As lower limb amputations are preventable, detection at an earlier stage is advisable. Most of the diabetic subjects are symptom free for PVD. Subjects with asymptomatic PVD not only have a higher risk for frank PVD but also an increased risk for cardiovascular deaths.[38] One of the easiest measures for detecting PVD is ankle brachial index [<0.9] measured by peripheral Doppler. This has been shown to have a sensitivity of 70 to 97% and specificity of 89 to 97%.[39,40] In addition, studies have shown ankle brachial pressure index to be a good predictor of subsequent cardiovascular events.[41,42] Sophisticated measures for assessing PVD include Duplex Doppler studies and angiography.

Coronary artery disease [CAD] can often be asymptomatic and early screening is therefore advantageous in preventing major events. Since diabetes is considered as a risk equivalent[43] for CAD routine screening for CAD in these patients is justified. The recommended initial test for routine screening for CAD is resting electrocardiography (ECG). This provides evidence of previous silent myocardial infarctions and silent or inducible myocardial ischemia. Cardiac stress test (Treadmill) is useful in detecting latent CAD but the test has a substantial false positive and false negative rates. Thallium-201 scintigraphy, exercise echocardiography, and ambulatory ECG are less commonly used for screening purposes. Another test, which is gaining importance in the field of cardiology, is measurement of carotid intimal medial thickness [IMT]. Several studies have indicated IMT to be a strong predictor for cardiovascular events.[44,45] IMT has been clearly shown to be higher among diabetic subjects compared to non-diabetic subjects.[46-48] IMT has also shown to be a good predictor for cerebrovascular disease.[49,50] However, this measurement requires a high-resolution ultrasound. Recently functional changes in the artery, which can be assessed by determining the endothelial dysfunction and arterial stiffness, have been shown to be indicative of future cardiovascular events.[47] These measurements also require sophisticated instruments like high resolution B mode ultrasonography system or Sphygmocor apparatus.

PREVENTION OF DIABETES COMPLICATIONS:

The metabolic consequences of diabetes include hyperglycemia, hypertension and dyslipidemia. Landmark trials and intervention studies have clearly documented the beneficial effects of glycemic control, blood pressure control and lipid control in delaying the onset of complications.

Glycemic control:

Hyperglycemia is responsible for many functional vascular changes, which include endothelial dysfunction, impairment of blood flow, increased leukocyte, monocytes adhesion etc. It also has many indirect metabolic effects that alter lipid patterns resulting in dyslipidemia. Evidence from various studies suggests a continuous relationship of hyperglycemia with microvascular complications (retinopathy and nephropathy) and neuropathy.[51-53] It has been shown that for every 1% decrease in glycosylated hademoglobin [HBA_{1c}] there is dramatic decrease in prevalence of complications (Figure 4). However, the effect of glycemia on macrovascular disease is not so clear.

Glycemic control and prevention of microvascular complications:

Three land mark studies on glycemic control in diabetes namely the Diabetes Complications and Control Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto study[27,28,54] have clearly documented the beneficial effects of glycemic control in preventing microvascular complications (Table 2).

The DCCT[27], a multicentric prospective study conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) involved 1,441 type 1 diabetic subjects in the age range 13 to 39 from 29 centres in the United States and Canada. Seven hundred and twenty six patients who had no retinopathy formed the primary prevention cohort and 715 subjects with mild to moderate retinopathy formed the secondary prevention cohort. These subjects were then randomized to either a conventional (710 patients) or intensive (726 patients) regimen of therapy and were followed for 3.5 to 9.0 years. A difference in glycosylated haemoglobin (HbA_{1c}) by 0.9% between the conventional and intensive therapy groups reduced retinopathy by 76%, albuminuria by 54% and neuropathy by 60%. The DCCT study subjects were followed four years later in the EDIC [The Epidemiology of Diabetes and its Complications] study after their intensive interventions were stopped,

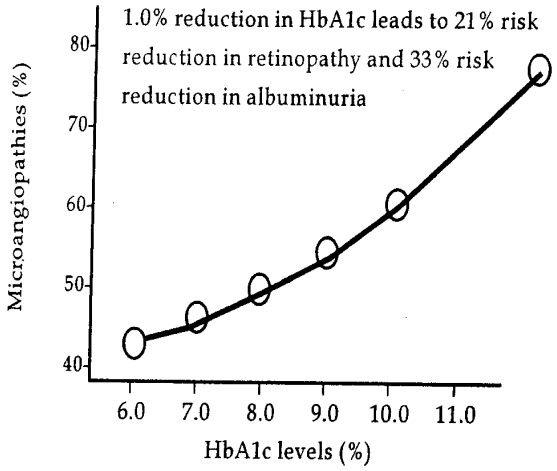

Fig. 4.Relation of glycemic control with microvascular complications

while the conventional therapy continued.[55] This study showed that although the HbA_{1c}'s of the two groups had become equal, those who were in the intensive group in the DCCT continued to do better with respect to complications. The Stockholm Diabetes Intervention Study (SDIS) on type 1 diabetic subjects based on a ten-year follow up showed a similar reduction in diabetic retinopathy with the intensive group having lower frequency of retinopathy compared to the conventional group.[56]

Two long-term studies on the type 2 diabetic subjects, the United Kingdom Prospective Diabetes Study (UKPDS) and the Kumamoto study showed clearly that intensive therapy decreased the risk of retinopathy compared to conventional therapy. The UKPDS.[28] recruited 5102 patients with newly diagnosed type 2 diabetes in 23 centers in the UK. The intensive therapy yielded 0.9% decrease in HbA1c level compared to the conventional. This decrease led to a risk reduction of 21% for retinopathy and 33% for albuminuria. The Kumamoto study[54] done on 110 Japanese type 2 diabetic subjects had two arms - the multiple insulin injection therapy (MIT) group (intensive group) who were administered three or more daily insulin injections or conventional insulin injection therapy (CIT). This study concluded that the glycemic threshold to prevent the onset and progression of diabetic microvascular complications as HbA_{1c}<6.5%, fasting plasma glucose concentration <110mg/dl, and 2-h postprandial plasma glucose concentration <180mg/dl.

The importance of continuous infusion of insulin to reduce symptomatic neuropathy was assessed in a four month follow up study which revealed achieving near normoglycemia in patients with symptomatic neuropathy achieved symptomatic and objective benefit.[36]

A meta analysis by Wang et al[57] on 16 randomized trials estimated the impact of glycemic control over progression of microvascular complications. It summarized that "long term intensive blood glucose control significantly reduced the risk of diabetic retinopathy and nephropathy".

Glycemic control and macrovascular complication:

Earlier studies in the western population like the Whitehall study, Honolulu Study, PADY study and several others have shown that hyperglycemia contributes to cardiovascular disease.[58-61] Indian studies have shown that the risk for CAD increases with increase in plasma glucose.[62-64] Hyperglycemia increases glycation of proteins resulting in advanced glycation end products [AGE]. AGE per se can trigger the atherosclerotic process, in addition, as the arterial wall components also get glycated, this leads to arterial stiffness and thence to vascular disorders. It could be postulated that glycemic control reduces non-enzymatic glycation, which in turn could reduce the occurrence of cardiovascular events. Several studies on antidiabetic agents, particularly thiazolidinediones have shown beneficial reduction in cardiovascular risk factors like LDL, fibrinogen, inflammatory markers and pre-clinical atheroslcerotdic markers.[65-67] A randomized double blind multicentric study conducted on over 3000 patients showed that pioglitazone effectively decreased triglycerides and increased HDL cholesterol both when used as monotherapy or in combination with metformin.[68] Furhter studies have also shown differential effects on lipid parameters with regard to glitazones, pioglitazones beneficially reduces triglycerides and particle concentration of LDL and increases HDL cholesterol compared to rosigligaxone.[69] In addition, the recent Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) study suggested that pioglitazone reduced main secondary endpoint of life-threatening events, the risk of heart attacks, strokes and death by 16% (p=0.027).[70] However, it reduced the primary endpoint of all cause mortality by only 10% which did not reach statistical significance by study end (p=0.095). However, in the UKPDS study, by glycemic control alone, the risk reduction of myocardial

Table 2. Glycemic control and risk reduction of microangiopathy in Intervention Studies

	DCCT (27) (Type 1 diabetes)	UKPDS (28) (Type 2 diabetes)	Kumamoto (54) (Type 2 diabetes)
Number studied	n = 1441	n = 5102	n = 110
Duration of follow up	9 years	10 years	6 years
Retinopathy	76%	21%	69%
Albuminuria	56%	33%	70%
Neuropathy	60%	-	57%

infarction was reduced by 16% but this just missed statistical significance [p=0.052] leading to the conclusion that by glucose control alone, macrovascular complications cannot be prevented.[28] Some of the reasons for this could be that the study was underpowered for macrovascular events, tight enough glycemic control was not established or that drugs like sensitizers were not used.[71] Though the DIGAMI[72] trial showed that 24-hour intensive treatment with intravenous insulin, glucose, and potassium followed by tight blood sugar control with insulin significantly reduced mortality, this study has several flaws and recent studies have not been able to confirm these findings.[73]

Though hyperglycemia plays a major role in complications, the consensus today is that to prevent macrovascular complications in diabetic patients tight control of factors like hypertension and dyslipidemia are equally important and these are described below. Table 3 summarizes the current evidence with respect of control of risk factors and prevention of diabetic complications.

Hypertension control:

Blood pressure is another key factor which can affects both micro as well as macro vasculature. Over 50% of type 2 diabetic subjects may have hypertension. It has been hypothesized that both type 2 diabetes and hypertension have common pathogenic mechanisms. Controlling blood pressure is an important aspect in treating complications, as untreated hypertension results in declining renal function.[74] In the PROCAM study, the prevalence of CAD was several fold higher in diabetic hypertensives compared to diabetic normotensives.[75] The risk for CAD in males with hypertension was two fold higher and in females four fold higher compared to normotensives.[75] Based on these and other studies, the goals recommended for blood pressure for diabetic subjects both by the ADA as well as the JNC VII are lower than those recommended for non-diabetic subjects.[76,77]

Hypertension control and microvascular complication:

Hypertension hastens the progression of diabetic retinopathy. Exudates were reported to be more among diabetic subjects with systolic blood pressure greater than 145 compared to those with less than 125 mm of Hg.[78] The UKPDS study also addressed the issue of hypertension control in reducing microvascular complications. A 10/5 mmHg reduction in blood pressure yielded a 34% reduction in risk of diabetic retinopathy.[79] The EUCLID study, which assessed the impact of lisinopril on microvascular complications in type 1 diabetic subjects, suggested a decrease in progression of retinopathy among the drug intervention arm compared to placebo (odds ratio: 0.50, p = 0.02).[80]

ACE inhibitors and angiotensin II receptor antagonists have been shown to have greater benefits in diabetic subjects in preventing progression of microalbumniuria to macroalbumniuria stage.[34,81-86] Further, ACE inhibition has been shown to be beneficial in diabetic subjects at all stages of nephropathy. In microalbuminuric patients, ACE inhibitors reduce the progression to macroalbuminuria and in macroalbuminuric patients, they reduce the decline in glomerular filtration rate [GFR].[81-86] Indeed ACE inhibitors slow

Table 3. Benefits of risk factor control on diabetes complications

Risk factor	Retinopathy	Nephropathy	Neuropathy	Macrovascular Diseases
Glucose control	Definite benefit	Definite benefit	Definite benefit	Possible benefit
Blood pressure control	Definite benefit	Definite benefit	Unknown value	Significant benefit
Lipid control benefit	Possible	Possible benefit benefit	Possible benefit	Significant
Smoking unclear	Benefits	Benefits unclear value	Unknown benefit	Significant

down the progression of nephropathy independent of their effects on blood pressure.[86] In the MICRO-HOPE study, which is a sub study of HOPE, 3,577 subjects with diabetes received either ramipril (10mg) or placebo. After a median follow-up period of 4.5 years, ramipril treatment was associated with a decreased risk of development of overt nephropathy.[35] Overall, hypertension control seems to be beneficial in reducing both nephropathy and retinopathy in diabetic subjects.

Hypertension control and macrovascular complication:

Though the UKPDS study failed to show a significant reduction in macrovascular end points with glycemic control, hypertension control yielded impressive results in reducing cardiovascular endpoints. Each 10 mm Hg decrease in mean systolic blood pressure was associated with 11% reduction for myocardial infarction.[79] In the HOT trial, 51% reduction in major cardiovascular events was observed in the target group with diastolic blood pressure £ 80 mm Hg compared to the group with £ 90 mm Hg.[87] The prevention of events from macrovascular disease seems to be dose dependant as subjects with greater blood pressure control were the most benefited.[88] Lisinopril was shown to reduce mortality in diabetic subjects with acute myocardial infarction in the GISS-3 study.[89] The CAPP study showed that captopril reduces cardiovascular mortality in subjects with hypertension.[90] Calcium channel antagonist like verapamil have also been shown to reduce reinfarction rates in diabetic subjects.[91] However, ACE inhibitors and beta-blockers appeared to be more beneficial than calcium channel blockers in reducing myocardial infarction.[71] The MICRO-HOPE study showed that ramipril reduced myocardial infarction by 22%, cardiovascular death by 37% and revascularization by 17%.[35] A summary of the studies, which have shown a remarkable reduction in cardiovascular mortality are depicted in Table 4.[86,92-95]

Dyslipidemia and microvascular disease

Dyslipidemia, particularly increased serum cholesterol and LDL cholesterol have been shown to be associated with diabetic retinopathy especially hard exudates in macula.[96-98] Abnormalities in serum lipid are hypothesized to alter the coagulation, fibrinolytic system, membrane permeability, endothelial dysfunction and thereby result in altered capillary blood flow leading to worsening of diabetic retinopathy and nephropathy. In addition, dyslipidemia also hastens the decline in glomerular filtration rate and progression of albuminuria to overt nephropathy.[99] A prospective study on 297 type 1 diabetic patients showed serum triglycerides to predict diabetic nephropathy and diabetic retinopathy.[100] Some intervention studies have shown lipid control could help prevent diabetic nephropathy[101], but not many studies have assessed its role in diabetic retinopathy. Although studies have shown serum lipids to be associated with microvascular complications the effect of intervention with lipid-lowering therapy has not been widely investigated.

Control of dyslipidemia and macrovascular disease:

Cross-sectional, prospective and interventional studies have consistently documented the association

Table 4. Antihypertensive Agents that Reduce Cardiovascular Risk in Patients with Type 2 Diabetes

Study	Drugs
Systolic Hypertension in the Elderly Program (SHEP)[92]	Diuretics: Chlorthalidone & β-blocker :Atenolol
Heart Outcome Prevention Evaluation (HOPE) (86)	ACE inhibitor - Ramipiril
United Kingdom Prospective Diabetes Study (UKPDS)[79]	ACE inhibitor: Captopril β-blocker : Atenolo
Appropriate Blood Pressure Control in Diabetes (ABCD)[93]	ACE inhibitor: Enalpril
Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trials (FACET)[94]	Ace inhibitor – Fosinopril
Losartan Intervention for End Point reduction in hypertension study (LIFE)[95]	Angiotensin receptor blocker: Losartan

of dyslipidemia with cardiovascular disease.[102-104] Lipid control plays a major role on the course of than that of microvascular disease. Several intervention studies have very clearly demonstrated the positive benefits of lipid control in cardiovascular disease.[71]

More than 50 clinical trials have supported the clinical benefit of cholesterol management in prevention of cardiovascular disease.[105-108] The role of simvastatin in reducing mortality rates was shown in the 4S trial conducted on 4444 subjects.[105] Both the LIPID and CARE studies demonstrated the effect of pravastatin and simvastatin in increasing survival.[106,107] In studies such as WOSCOPS and AFCAPS use of pravastatin in subjects without CVD showed a 25% reduction in CVD rates on follow up.[108,109] Most of these studies had sub studies on diabetic subjects, which indicated that diabetic subjects more markedly benefited by cholesterol reduction compared to the non-diabetic.[71] The data on risk reduction of cardiovascular events in diabetic subjects from various trials are presented in table 5. The Heart Protection Study included 5,963 adults aged 40-80 years with diabetic subjects of whom 90% were type 2 diabetic subjects. The mean LDL cholesterol level was reduced from 125mg/dl to 86 mg/dl and this reduction yielded a 22% reduction of major cardiovascular events in the Simvastatin group compared to the placebo-allocated group. There was also a 33% reduction in events among diabetic subjects without evident cardiovascular disease at baseline.[110]

Another class of drugs, the fibrates has been shown to markedly reduce triglycerides and moderately elevate HDL cholesterol and thereby reduce cardiovascular events.[108-111] In the VA-HIT study gemfibrozil significantly increased HDL levels resulting in remarkable decrease in the incidence of myocardial infarction.[111] The Helsinki Heart Study and Bezafibrate Infarction Prevention Trial and Diabetes Atherosclerosis Intervention Study (DIAS) are the other major trials which have shown fibrates to be protective[112-114] (Table 5).

Multi-factorial approaches to prevention of CVD in diabetics:

Although in clinical practice, most diabetologists advie simultaneous control of blood glucose, blood pressure and lipids so as to take care of all the above mentioned risk factors, there were no studies on the effect of tackling all these risk factors on macrovascular complications until the recent Danish Steno 2 study.[115]

The Steno 2 study had two arms, the conventional and intensive group with eighty type 2 diabetic individuals in each. The treatment regimen focused on glycemic control, hypertension control, lipid control and antiplatelet therapy, with the intensive group having a lower target than the conventional group. After a mean follow up of 7.8 years, the outcomes, which included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization, and amputation, were assessed. There was a significant decrease in the

glycosylated hemoglobin values, systolic and diastolic blood pressure, serum cholesterol and triglyceride levels in the intensive group compared to conventional group. This decrease resulted in lower risk of cardiovascular disease, nephropathy, retinopathy, and autonomic neuropathy. The cardiovascular event rate in conventional-therapy group was 44% compared to 24% in the intensive group. Overall, in the intensive group there was a significant reduction in cardiovascular disease (CVD) with a hazard ratio of 0.47 in 7.8 years of follow up. This risk reduction was statistically significant even after adjusting for baseline duration of diabetes, age, sex, smoking status, and presence or absence of cardiovascular disease. The risk reduction in cardiovascular events observed in this study is higher than other studies, which have used single-factor intervention strategies, targeting glycemic control, hypertension control or lipid control.

Patients receiving intensive therapy also had a significant reduction in CVD (hazard ratio, 0.47; 95 percent confidence interval, 0.24 to 0.73), nephropathy (hazard ratio, 0.39; 95 percent confidence interval, 0.17 to 0.87), retinopathy (hazard ratio, 0.42; 95 percent confidence interval, 0.21 to 0.86), and autonomic neuropathy (hazard ratio, 0.37; 95 percent confidence interval, 0.18 to 0.79). Results from this study emphasised the need for a multi-factorial approach to present cardiovascular disease in diabetic subjects.

Life style measures:

Life style changes like dietary modification, regular exercise and cessation of smoking has been suggested as measures to reduce cardiovascular disease.[116] One of the most important modifiable risk factor for prevalence of both PVD and CAD is cessation of smoking. One of the life style intervention programme which included smoking cessation showed clinical benefits for subjects with PVD.[117] Cessation of smoking has been constantly emphasized particularly in subjects with high risk for vascular disease.[117,118]

Though dietary modification is always a challenge as the dietary patterns differ in different countries, there are a few strategies, which could be of benefit to everyone. 1) Type of fat: substituting saturated fat and trans- fatty acids with non-hydrogenated mono-and poly-unsaturated fats 2). Improving quality of carbohydrate: Substitute high glycemic index (GI) foods with low GI ingredients and increase intake of cereals rich in fibres. 3) Reduce salt intake.[119]

Physical activity has shown to have a strong relation with coronary artery disease.[116] A prospective study on 8302 Finnish men and 9139 women aged 25 to 64 years without a history of antihypertensive drug

Table 5. Lipid lowering Agents that reduce cardiovascular risk in patients with Type 2 diabetes

Study	Drugs	Risk reduction
Statin trials		
Scandinavian Simva Statin Study [4S][105]	Simvastatin	55%
Long-term Intervention with Pravastatin in Ischemic Disease (LIPID)[106]	Pravastatin	19%
Cholesterol and Recurrent Events (CURE)[107]	Pravastatin	25%
Air Force / Taxes Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[109]	Lovastatin	43%
Heart Protection Study (HPS)[110]	Simvastatin	22%
Fibrate trials		
Veterans Administration High density lipoprotein Intervention trial [VA-HIT][111]	Gemfibrozil	24%
Helsiniki Heart Study [HHS][112]	Gemfibrozil	68%
Bezafibrate Infraction Prevention Study (BIP)[113]	Bezafibrates	42%
Diabetes Atherosclerosis Intervention Study [DAIS][114]	Fenofibrate	23%

use, coronary heart disease, stroke, and heart failure at baseline showed that subjects with heavy grade of physical activity had low prevalence of hypertension.[116] Exercise helps in weight reduction and also reduces cholesterol levels which would prevent vascular disorders.

A multi-drug approach coupled with life style measures would be ideal to prevent the onset of complications. However, once complications set in, specific measures to tackle the consequences of the complications have to be incorporated into the patient's treatment regimen.

Intermediate approach for prevention of diabetes complications:

These approaches are specific for diabetes related complications as suggested in Table 6.

Diabetic retinopathy: The Diabetic Retinopathy Study [DRS] assessed the effect of pan-retinal photocoagulation on the risk of vision loss from PDR. Photocoagulation significantly reduced visual loss and this effect persisted throughout the entire follow up.[120] The ETDRS study investigated the timing for initiating photocoagulation and suggested that scatter photocoagulation be deferred in eyes with mild to moderate non-proliferative diabetic retinopathy.[29] By timely screening for retinopathy and aggressive use of photocoagulation both the sight threatening forms of retinopathy namely proliferative diabetic retinopathy and microaneurysms can be effectively tackled.

Diabetic nephropathy: The measures taken for regressing the progression of diabetic nephropathy include tight blood pressure control, use of ACE inhibitors, and protein restriction in diet.[121] Protein restriction in type 1 diabetic subjects reduced the decline in glomerular filtration rate.[122] Similarly, creatinine clearance decreased more slowly in subjects with low protein diet compared to those on high protein diet.[122]

Diabetic neuropathy: Nearly 5% of painful peripheral neuropathy in diabetic subjects could be due to non-diabetic causes. The management of symptomatic neuropathy is given in Table 7. For painful peripheral neuropathy, the drug recommended is tricyclic antidepressant drugs, phenytoin, carbamazepine and topical capsaicin.[36] NSAIDS should be used with caution as these could be of great risk in subjects with renal insufficiency. The new drugs in market like the gamma as these linolenic acid and alpha lipoic acid and methylcobolamine have been reported to be of some benefit.

Macrovascular diseases: Drugs, which are considered to be of great use in preventing cardiovascular diseases, include aspirins and anti-

Table 6. Strategies for prevention of diabetes complications

Complication	Early approach	Intermediate approach	Late approach
Diabetic retinopathy	Glycemic control Blood pressure control Lipid control	Photocoagulation	Vitero-retinal Surgery
Diabetic nephropathy	Glycemic control Blood pressure control Lipid control	ACE inhibitors	Dialysis Transplantation
Peripheral neuropathy	Glycemic control Foot wear	Gamma Linolenic acid Alpha lipoic acid Drugs for relief of pain	Prompt intervention (antibiotic, local surgery) Custom made foot wear Corrective surgeries
Macrovascular disease	Glycemic control Blood pressure control Lipid control	Antiplatelet drugs	Revascularization Surgery

Table 7. Management of symptomatic neuropathy

Steps	Action
1	Exclude non-diabetic causes
2	Explanation and education to the patient
3	Tight glycemic control
4	Consider symptomatic therapy

	Drug class	Drug
	Tricyclics	Amitriptyline Imipramine
	Anticonvulsants	Gabapentin Lamotrigine Carbamazepine
	Antiarrhythmics	Mexilitiene
	Other agents	Tramadol
	Topical application	Capsaicin

platelet drugs like GP IIb/IIIa inhibitors. The CURE study on 12,562 patients with acute coronary syndrome using aspirin demonstrated that adding Clopidogrel to aspirin effectively prevents the combined incidence of cardiovascular death, myocardial infarction, or stroke.[123] Indeed diabetic subjects had more benefit by using GPIIb/IIIa inhibitors compared to non-diabetic subjects according to a meta analysis on 6 large studies which involved 23,072 patients without and 6,458 patients with diabetes admitted for non-ST-segment elevation myocardial infarction or unstable angina.[124]

Late approach for prevention of diabetes complications:

This forms the last step and is used in the end stages of the diabetes complication. The late approaches have been sequenced in Table 6. Viterio-retinal surgery is used to regain sight in those with bleeding due to proliferative retinopathy and in cases of retinitis proliferans and retinal detachment. Dialysis and kidney transplantation are used in end stage renal failure with good results. In macrovascular disease, intervention like angioplasty and by pass surgery have been used with varying degrees of sucess. New types of stents like the drug-eluting stents are considered to be major breakthroughs in preventing restenosis.[125] However, it can be appreciated that most of these are not curative but palliative therapies and it is better to try to prevent patients going into these late stages of complications.

Future perspectives:

With rapid advances in the field of diabetology, newer drugs are now in the pipeline, which could specifically address the consequences of complications. For diabetic retinopathy, protein kinase C inhibitors and similar products may form the basis of future treatments for diabetic retinopathy.[126] Ruboxistaurin (LY333531) a compound that shows a high degree of specificity over the protein kinase C (PKC) gene family for inhibiting PKC beta isoforms is considered to be useful in preventing microvascular complications.[127] The potentials of aldose reductase inhibitors and antioxidant therapy in preventing complications are also under study.[36] For preventing cardiovascular and cerebrovascular diseases new generation statins and fibrates may be more effective than at present.

Owing to the importance of multi-factorial approach to drugs, poly pharmacy is the rule. An important task for the pharmaceutical industry is to try to develop combinations of drugs that are safe and effective thereby helping the diabetic patient to live an easier, longer and healthier life despite diabetic.

SUMMARY

- Both the economic burden and loss quality of life experienced by a diabetic individual could be attributed to its morbidity associated with microvascular and macrovascular complications.
- The natural history of type 2 diabetes provides chances for prevention at three transition points: primary prevention of diabetes itself, secondary prevention-early detection to prevent onset of complications and tertiary prevention-retardation of progression of complications and prevention of disability.
- Early detection of diabetic complications by routine screening is an important aspect in prevention of diabetes complications. Annual screening is recommended for all diabetic patients for all complications. This includes retinal screening for detecting retinopathy, microalbumniuria for diabetic nephropathy, examination of pedal pulses and peripheral doppler for peripheral vascular disease, 12 lead electrocardiography for coronary artery disease and if indicated Treadmill

and Echocardiography as well as a complete foot examination including monofilament testing and biothesiometry for diabetic neuropathy.

- The early approaches for prevention of complications should target glycemic control, hypertension control and control of dyslipidemia. Such a multifactorial approach is necessary to prevent complications, particularly macrovascular disease.
- Life style measures to prevent complications should include dietary modification, which includes substituting (i) saturated fat, and trans- fatty acids with non-hydrogenated mono-and poly-unsaturated fats (ii) high glycemic load items with low glycemic items, increasing fiber intake and reducing salt intake. Regular exercise and cessation of smoking would also help in preventing macrovascular complications.
- The intermediate approach should target prevention of progression of complications after the complications set in. This includes pan-retinal photocoagulation for reducing the risk of visual loss in subjects with retinopathy, tight blood pressure control and protein restriction in subjects with nephropathy and use of antiplatelet therapy for macrovascular disease.
- Late approach includes interventional procedures to prevent progression to end stage of the complications, like vitreo-retinal surgery (proliferative retinopathy), dialysis and kidney transplantation (renal failure) angioplasty and bypass surgery (macrovascular disease).

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