Review Article

Occurrence, Complications, and Interventions of Diabetes: A New Understanding of an Old Problem

Rambhade SK, Singh S[1], Goswami RB[1], Rambhade A[1]

Department of Pharmacology, Peoples Institute of Pharmacy and Research Center, Peoples Hospital, Ayodhya By-Pass Road, Bhopal, MP, [1]Department of Pharmacology, Sagar Institute of Research Technology and Science Pharmacy, near ISRO, Ayodhya Nagar, Bhopal, MP-462 041, India

ARTICLE INFO

Article history:
Received 10 January 2011
Accepted 30 March 2011
Available online 02 August 2011

Keywords:
Diabetes
Diabetic complications
Oxidative stress
Polyol pathway
Protein kinase C

ABSTRACT

This review aims to summarize the major advances of the preceding year and to put them into the context of current opinion on diabetes mellitus. Despite the advent of life-prolonging insulin for the treatment of diabetes, the appearance and progression of many of the disabling complications associated with this disease cannot be prevented through the administration of insulin. Clinically, the onset and rate of progression of diabetic complications, including cataract, corneal epitheliopathy, microangiopathy, nephropathy, neuropathy, and retinopathy, appear to be dependent upon both the duration and the severity of the diabetes. This review summarizes the specific pathogenic mechanisms of microvascular complications for which clinical therapies have been developed, including the polyol pathway, advanced glycation end products, protein kinase C, vascular epithelium growth factor, and the superoxide pathway. The review further focuses on therapies for these targets that are currently available or are undergoing late-stage clinical trials.

Introduction

Diabetes has been a mass killer on globe for quite a long time now. There have been several previous estimates of the number of persons with diabetes. The World Health Organization (WHO) published estimates for the years 2000 and 2030, using data from 40 countries but extrapolated to the 191 WHO member states.[1] WHO estimates that more than 180 million people worldwide have diabetes; this number is likely to more than double by 2030.[2] Shaw *et al.* estimates suggest that in 2010, there are 285 million people worldwide with diabetes, with considerable disparity between populations and regions. The study estimate for 2010 of 285 million adults with diabetes is 67% higher than the 2004 published estimate for the year 2000[3] and Shaw *et al.* 2030 estimate of 439 million is 20% higher than the same study's estimate for 2030.[1] In 2005, an estimated 1.1 million people died from diabetes. Almost 80% of diabetes deaths occur in low- and middle-income countries.[2] WHO projects that diabetes death will increase by more than 50% in the next 10 year without urgent action. The global increase in diabetes will occur because of population ageing and growth and because of increasing trends toward obesity, unhealthy diets, and sedentary lifestyles.[4] In developed countries, most people with diabetes are above the age of retirement, whereas in developing countries, those most frequently affected are aged between 35 and 64 years.[2]

Chronic diabetic complications constitute a group of diseases responsible for substantial morbidity and mortality, and prevention of such complications is a key issue in the management of the diabetes epidemic.[5-7] Therapeutic modalities for diabetes have evolved a great deal. However, most people with this disorder go on to develop complications leading to damage to various body tissues. These complications include diabetic retinopathy (DR), nephropathy, neuropathy, cardiomyopathy, and macroangiopathic complications such as atherosclerosis.[8,9] The macrovascular complications are not diabetes specific but are more pronounced in diabetes. Diabetic complications arise primarily because of hyperglycemia-induced metabolic changes, leading to changes in the structural and functional properties of macromolecules.[10,11]

Access this article online	
Website: www.sysrevpharm.org	**Quick Response Code:**
DOI: 10.4103/0975-8453.83433	

Correspondence:
Mr. Ashish Rambhade; E-mail: sujitrambhade@gmail.com

Frequency of Complications

Among people with diabetes, about 15% have type 1 (formerly known as insulin-dependent diabetes), while about 85% have type 2 diabetes (formerly known as non-insulin-dependent diabetes). In type 1, there is β cells that are detectable in blood, but some are idiopathic (type 1B)– no β cell antibody is found. In all type 1 cases, circulating insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition. In type 2 diabetes, a moderate reduction in the β cell mass has been reported, though in some cases, reduction in β cell mass was not observed.[12,13]

In contrast, type 2 diabetes is usually part of the "metabolic syndrome" which is associated with other risk factors from early in the disease process, including abdominal obesity, hypertension, dyslipidemia, prothrombotic state, and insulin resistance.[14] Macrovascular disease is a major cause of morbidity and mortality in type 2 diabetes; microvascular complications are often present when diabetes is diagnosed, even in people with no symptoms.[15-18]

Clinical Complications of Diabetes Mellitus

Retinopathy

Diabetes mellitus (DM) is a major cause of avoidable blindness in both the developing and the developed countries. After 15 years of diabetes, approximately 2% of people become blind and about 10% develop severe visual impairment.[2] Patients with DR are 25 times more likely to become blind than nondiabetics.[19] Good glycemic control arrests the development and progression of DR and decreases the visual loss.[20] Technological advances have improved the diagnostic accuracy of screening methods and access of the diabetic patients to the specialist care. In the last three decades, the treatment strategies have been revised to include early surgical interventions and pharmacotherapies, besides laser photocoagulation.[21-23]

DR is classified in various progressive stages, namely, nonproliferative (background) retinopathy, preproliferative (severe or advanced background) retinopathy, and proliferative retinopathy. The retina is comprised of several tissue types, including neural tissue with respective support cells and vascular tissue.[24]

DR predominantly affects the vascular components of the retina. Pathological changes in background DR include capillary basement membrane thickening, pericyte loss, microaneurysms, acellular capillaries, increased capillary permeability with exudate deposits, and retinal microinfarcts.[24,25] In advanced proliferative retinopathy, neovascularization develops with its devastating consequences.[10,25]

The final metabolic pathway causing DR is unknown. There are several theories. Electrolytic imbalance caused by the high aldose reductase (AR) levels leads to cell death, especially retinal pericytes, which cause microaneurysm formation.[26] Apart from this, thickening of the capillary basement membrane and increased deposition of extracellular matrix (ECM) components contribute to the development of abnormal retinal hemodynamics.[27] In diffuse type of diabetic macular edema (DME), breakdown of the inner blood-retinal barrier results in accumulation of extracellular fluid. Increased retinal leukostasis has been reported and it causes capillary occlusions and dropout, nonperfusion, endothelial cell damage, and vascular leakage due to its less deformable nature. Currently, there has been a great interest in vasoproliferative factors which induce neovascularization. It has been shown that retinal ischemia stimulates a pathologic neovascularization mediated by angiogenic factors, such as vascular endothelial growth factor (VEGF), which results in proliferative DR.[28,29] VEGFs are released by retinal pigment epithelium, pericytes, and endothelial cells of the retina.[19,30]

Nephropathy

Diabetes is among leading causes of kidney failure. Ten to twenty percent of people with diabetes die of kidney failure.[2] Diabetic nephropathy affects approximately 30% of type 1 diabetic patients. Diabetes remains the most important cause of renal failure in industrialized countries.[31-33] Type II diabetes and diabetic nephropathy are clearly chronic progressive diseases that are associated with a combination of genetic, lifestyle, and environmental factors.[34] Although many risk factors have been identified, such as obesity, diet, and other lifestyle factors, it is highly likely that there are as yet unidentified environmental factors that influence whether or not an individual will become diabetic, or whether mild or incipient diabetes progresses to a more advanced disease state.[35-37]

Glomerular hyperfiltration leading to microalbuminuria is the earliest clinical marker of this disease. With progression of renal damage, patients develop macroalbuminuria and reduced glomerular filtration rate.[38,39] Pathological features of diabetic nephropathy include mesangial matrix expansion, thickening of glomerular capillary basement membrane, and tubulointerstitial fibrosis.[35,40] In earlier stages, however, there is renal enlargement due to cellular hypertrophy affecting both the glomeruli and tubules. Eventually, the glomerular filtration rates continue to decline and the patients develop arteriolosclerosis and glomerulosclerosis with obliteration of the filtration area due to increased production and decreased degradation of ECM proteins. In the later stages, patients develop characteristic nodular accumulation of ECM proteins, that is, Kimmelstiel-Wilson nodules.[41] Clinically, overt nephropathy manifests as proteinuria in the nephritic range, hypertension, and other features of renal failure.[42] It has been demonstrated that similar to other chronic complications, a high blood glucose level is the initiating factor leading to the development of renal damage in diabetes.[43,44] Furthermore, it has been demonstrated that good glucose control may even reverse the structural changes in the kidneys.[43]

Identification of patients at high risk by screening for microalbuminuria now occurs in many hospital clinics and potentially early and effective antihypertensive treatment in these patients can postpone or prevent clinical nephropathy. Blockade of the rennin-angiotensin system by angiotensin I-converting enzyme inhibitors may decrease microalbuminuria in normotensive diabetic patients independently of the fall in blood pressure.[10,45]

Neuropathy

According to WHO, Diabetic neuropathy is damage to the nerves as a result of diabetes, and affects up to 50% of people with diabetes. Although many different problems can occur as a result of diabetic neuropathy, common symptoms are tingling, pain, numbness, or weakness in the feet and hands.[2] Both the somatic and autonomic nervous system can be affected by diabetes, causing a variety of symptoms.[46,47] At the severe end of the spectrum, diabetic nerve

disease is a major cause of lower extremity amputation.[48]

It has been reported that inflammation is more clearly involved in the specific inflammatory neuropathies such as vasculitic and granulomatous disease than in diabetic neuropathy,[19,49] though it has not been studied in age-related neuropathies. P and E-selection, activated during the inflammatory process, predict the decline in peripheral nerve function among diabetic patients.[21] Impaired blood flow and endoneurial microvasculopathy, mainly thickening of the blood vessel wall or occlusion, play a critical role in the pathogenesis of diabetic neuropathy. Metabolic disturbances in the presence of an underlying genetic predisposition cause reduce nerve perfusion.[50]

Oxidative stress-related mechanisms are also important in vascular dysfunction, and tend to increase vasoconstriction.[51] Sensory and local autonomic nerve function deficits appear to predominate in patients with critical limb ischemia. Improving blood flow to tissues may improve nerve conduction velocity in diabetic neuropathy.[50,52] Oxidative and nitrosative stress and inflammation are implicated in several neurodegenerative disorders including Alzheimer's disease and amyotrophic lateral sclerosis. It is greater in diabetic patients prior to development of peripheral neuropathy and particularly in those with peripheral neuropathy.[52,53]

Retrospective and prospective studies have suggested a relationship between hyperglycemia and the development and severity of diabetic neuropathy, and significant effects of intensive insulin treatment on prevention of neuropathy.[54]

Low-dose tricyclic antidepressants, anticonvulsants (gabapentin, pregabalin, carbamazepine, and potentially phenytoin), serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine), topical analgesic (topical capsaicin), and various oral pain medications are agents that are currently available for the treatment of diabetic neuropathy.[55,56]

Cardiomyopathy

Diabetes increases the risk of heart disease and stroke and nearly 50% of people with diabetes die of cardiovascular disease (CVD).[2] Cerebrovascular disease (CeVD) represents a major cause of morbidity and mortality worldwide. The more overweight an individual is, the more likely he or she will be insulin resistant and will face an increased risk for developing all the associated abnormalities such as hypertension, type 2 DM, and CVD, including stroke.[57,58] DM, hypertension, smoking, dyslipidemia, atrial fibrillation, and physical inactivity are important risk factors for stroke, and their management with lifestyle modifications and pharmacological treatment can reduce stroke-associated morbidity and mortality in the general population.[56,59,60]

Diabetic cardiomyopathy can act as an independent factor affecting the cardiac structure and function and may also modulate prognosis of other complications such as ischemic heart disease.[61] It was demonstrated that diabetic patients had larger mean diameters of ventricular myocardial cells and higher percentage of interstitial fibrosis than control subjects.[62] Morphological changes in diabetic cardiomyopathy include myocyte hypertrophy and/or necrosis, interstitial and perivascular fibrosis, and capillary basement membrane thickening.[63] Functional abnormalities involve both the systolic and diastolic properties of the myocardium, such as impaired relaxation, reduced compliance with elevated end-diastolic pressure, cardiac hypertrophy, and chamber dilatation.[64]

The overall relative risk of stroke is 1.5 to 3 times greater in patients with DM,[65-67] while the relative risk for stroke is 10 times higher in diabetic patients younger than 55 years.[68] Recurrent stroke is also twice more frequent in diabetic patients.[69] More importantly, both short- and long-term mortality after stroke are significantly greater in diabetic patients.[70] Overall, the outcome of CeVD in patients with DM is worse than in nondiabetic patients. The principal mechanisms by which DM can lead to microvascular damage and finally CeVD are the following:

1. Increased production of free oxygen radicals and oxidative stress.[71]
2. Increased production of glycosylated products.[72]
3. Increased activity of AR in the polyol pathway, leading to intracellular accumulation of sorbitol and fructose.[71]
4. Activation of specific protein kinase C (PKC) isoforms.[73,74]

Formation of reactive oxygen species (ROS) due to hyperglycemia and insulin resistance leads to cell damage.[75] Free oxygen radicals decrease the bioavailability of endothelium-derived nitric oxide resulting in vasoconstriction, platelet activation, and smooth muscle cell proliferation. Activation of specific isoforms, especially PKC β and PKC δ, leads to cell proliferation, impaired glucose and lipid metabolism, expression of atherosclerosis-promoting genes, decreased vasodilation, and increased vascular permeability.[73,74]

Proposed guidelines for the early management of hyperglycemia during ischemic stroke[76] are as follows:

1. Initiate insulin therapy when plasma glucose is >140 to 180 mg/dl.
2. Therapeutic target: plasma glucose 80 to 140 mg/dl.

The recommendations on acute stroke are the following:

1. Critically ill patients: plasma glucose close to 110 mg/dl and always <180 mg/dl.
2. Non-critically ill patients: plasma glucose 90 to 130 mg/dl and postprandial plasma glucose <180 mg/dl.[76]

Macroangiopathy

Clinical manifestations of atherosclerosis occur primarily in three vascular beds: coronary arteries, lower extremities, and extracranial carotid arteries. Diabetes increases the incidence and accelerates the clinical course of each. The abnormal metabolic state that accompanies diabetes causes arterial dysfunction.[63,77]

Relevant abnormalities include chronic hyperglycemia, dyslipidemia, and insulin resistance. These factors render arteries susceptible to atherosclerosis. Diabetes alters function of multiple cell types, including endothelium, smooth muscle cells, and platelets, indicating the extent of vascular disarray in this disease[78] [Table 1].

Table 1: Complications of diabetes

Macrovascular diseases	Microvascular diseases
Transient ischemic attack	Diabetic retinopathy
Stroke	Nonproliferative
Angina	Proliferative
Myocardial infarction	Macular edema
Cardiac failure	Microalbuminuria
Peripheral vascular disease	Macroalbuminuriaw
	End-stage renal disease
	Erectile dysfunction
	Autonomic neuropathy
	Peripheral neuropathy
	Osteomyelitis
	Amputation

Concepts of Diabetic Complications

Diabetic complications arise primarily because of hyperglycemia-induced metabolic changes, leading to changes in the structural and functional properties of macromolecules.[79] Recent advances have identified secondary factors that play key roles in the development and progression of these complications. Some of the factors that participate in the pathogenesis of diabetic complications include polyol pathway, PKC activation, nonenzymatic glycation, oxidative stress, and alterations in growth factor and vasoactive factor expression. Several of these factors may subsequently lead to further endothelin (ET) activation in diabetic subjects.[2,80]

Polyol pathway

The polyol pathway reduces toxic aldehydes generated by ROS to inactive alcohols.[80,81] AR, through the consumption of NADPH, is responsible for the initial and rate-limiting step in the process. Glucose can be reduced to sorbitol, and eventually fructose, through this pathway, but AR has a low affinity for glucose at normal concentrations. Elevated intracellular glucose can increase AR activity, resulting in significantly decreased NADPH. NADPH is also required for glutathione (GSH) reductase activity, which reduces GSH—a major mechanism for reducing intracellular oxidative stress.[82] Decreased NADPH and resulting decreased GSH reductase activity ultimately increases oxidative stress and activates pathways that increase cellular damage.[6,24,83]

AR inhibition (ARI) is ostensibly an ideal target for reducing the deleterious effects associated with polyol pathway activation. However, clinical trials with ARIs have shown lack of efficacy or adverse effects.[84,85]

Nitric oxide (NO) and oxidative stress

DM was found to be inextricably connected with increased oxidative stress both in diabetic humans and hyperglycemic animals.[86,87] The term oxidative stress often refers to a biological redox condition where excessive oxidative modifications of cellular constituents occur due to increased oxidizing power.[88] Production of ROS (free radicals) may result from glucose autooxidation, protein glycation, increased flux through the polyol pathway, and prostanoid productions.[31] NO is a potent vasodilator formed from L-arginine by NO synthase.[89] NO released from endothelial cells acts on smooth muscle cells to increase intracellular cGMP and cAMP. The result of this increase in cGMP and cAMP is decreased calcium, probably through efflux, and dephosphorylation of myosin light chains. Endothelial dysfunction is characterized by the imbalance between contracting and relaxing factors.[87]

A disturbance in the cellular redox balance is assumed to interfere with the proper maintenance of cellular homeostasis.[28] Oxidative stress is an ineluctable consequence of aerobic metabolism, because free radicals and other reactive species are the products of normal metabolism, utilizing the redox potential to process cellular reactions.[30] Among the number of mechanisms proposed as a pathogenic link between hyperglycemia and diabetic complications, oxidative stress is an equally tenable hypothesis as the Maillard advanced glycation hypothesis or the AR-mediated osmotic hypothesis.[90,91]

Normalization of glucose-stimulated superoxide production has been found to block at least three independent pathways of hyperglycemia-induced vascular damage.[33,92]

Protein kinase C activation

PKC family of enzymes is activated by the diacylglycerol resulting from receptor-mediated hydrolysis of inositol phospholipids. PKC participates in a variety of functions, including signal transduction, regulation of ion channels and neurotransmitter release, control of cell growth and differentiation, and changes in cell morphology and gene expression.[40,74]

PKC activation assumes a central role in hyperglycemia-induced vascular disorders. High glucose concentrations can induce the production of diacylglycerol and activation of PKC.[93,94] PKC activation has been implicated in hyperglycemia-induced vascular permeability and flow changes, expansion of ECM, and in the production of various growth factors and cytokines.[95] The changes are seen as thickening of the basement membrane, increased retinal vascular permeability, and alterations in retinal blood flow.[31]

Research into novel therapeutic agents for diabetic kidney disease focused early on PKC because hyperglycemia, the defining feature of diabetes, increases diacylglycerol, advanced glycation end products (AGEPs), and oxidative stress. When production of these aberrant metabolic products is excessive, PKC is over activated, particularly in organs that are susceptible to developing diabetic micro- and macrovascular complications.[32,96]

Advanced glycation end products (AGEPs)

AGEPs are a heterogeneous group of modified proteins, lipids, and nucleic acids implicated in the aging process and diabetes.[97,98] Some AGEPs are exogenous, being derived from foods or even tobacco,[99] although their significance in diabetic pathology remains unclear. More than a dozen AGEPs have been detected in tissues and can be divided into the following three categories:[100]

1. Fluorescent cross-linking AGEPs such as pentosidine and crossline.
2. Nonfluorescent cross-linking AGEPs such as imidazolium dilysine cross-links, alkyl formyl glycosyl pyrrole cross-links and arginine-lysine imidazole cross-links.
3. Non-cross-linking AGEPs such as pyrraline and N-carboxymethyl lysine.

In intracellular hyperglycemia, these products are formed primarily through nonenzymatic reactions (Maillard reactions) between amino groups and glucose or highly reactive glucose derivatives known as dicarbonyls.[101] Hyperglycemia may also drive AGEP formation through polyol pathway-derived intermediates and oxidative stress.[6] AGEPs alter intracellular and extracellular proteins and their functions.[101,102] Studies in diabetic populations show AGEPs and nonenzymatic glycation correlate with the development and severity of retinopathy, neuropathy, and nephropathy, as well as macrovascular complications.[6,103] Glucose, fructose, and the product of the pentose phosphate pathway may participate in nonenzymatic glycation.[72-74] AGEs may further increase oxidative stress and endothelial damage.[98-100] Exogenous administration of superoxide dismutase has been shown to reduce hyperglycemia-induced endothelial permeability and accompanying vascular dysfunction. In addition, AGEs can form cross-links with collagen in the ECM, reduce arterial compliance, and alter gene expression of several important intracellular molecules.[2,104] Both AGEs and their receptors have been localized to the target organs of diabetic complications.[98,99]

These receptors are found on many cells, including endothelial and smooth muscle cells. AGE-mediated nuclear factor NF-κB activation has been shown to increase ET-1 expression.[99,100] Activation of NF-κB, secondary to nonenzymatic glycation, has also been linked to reduce NO, which would positively affect ET expression causes of diabetes complications.[99,105]

Vascular endothelial growth factor and angiopoietin (VEGF)

VEGF and the angiopoietins are two families of growth factors believed to act predominantly on vascular endothelial cells. VEGF is mitogenic for endothelial cells, acting early and at most points in the angiogenic cascade.[106,107] Increasing evidence suggests a role for VEGF in the pathophysiology of CVD.[108] Elevated plasma VEGF has been shown in patients with hypertension and diabetes, with levels correlating with measures of endothelial damage/dysfunction and overall cardiovascular risk in hypertensive patients. Furthermore, VEGF has independent prognostic significance in patients with acute coronary syndromes.[108] In contrast to VEGF, the angiopoietins have little effect on endothelial proliferation.[2] More recent data suggest that the angiopoietins may also be involved in the regulation endothelial integrity and inflammation.[109-111] Hence, selective increase in plasma VEGF and Ang-2, but not Ang-1, may favor aberrant neovascularization and endothelial abnormalities. However, there is no data on plasma angiopoietins and the relationship with inflammation and endothelial damage/dysfunction in patients with type 2 diabetes, with and without CVD.[90,100]

Hexosamine pathway

Glutamine: fructose-6-phosphate amidotransferase (GFAT), the enzyme catalyzing the synthesis of glucosamines, is the rate-limiting enzyme of this pathway. GFAT converts the fructose-6-phosphate to glucosamine-6-phosphate and finally to uridine diphosphate-N-acetylglucosamine.[112,113]

This Glucosamine-6-phosphate, produced by the hexosamine biosynthetic pathway, inhibits activity of glucose-6-phosphate dehydrogenase (G6PD), the rate limiting enzyme in the pentose shunt pathway.[113] Since G6PD activity is coupled to reduction of NADP+ to NADPH, activation of the hexosamine biosynthetic pathway would further decrease NADPH/NADP+ ratios. Decreased NADPH/NADP+ ratios, resulting from inhibition of G6PD or stimulation of NADPH oxidase, can increase oxidative stress by the following two mechanisms:

A. By decreasing the regeneration of the important cellular antioxidant, that is, reduced GSH from oxidized GSH (GSSG).
B. By decreasing availability of NADPH, thereby decreasing activity of catalase, the enzyme responsible for converting the H_2O_2 to H_2O. Indeed, GSH scavenging activity and NADPH content are decreased in vascular endothelial tissues by high glucose conditions.[114]

Prevention of Diabetes

The relationship between hyperglycemia with microvascular and macrovascular complications are now clear. Diabetes management seeks to prevent the microvascular (e.g., retinopathy, neuropathy, and nephropathy) and macrovascular (e.g., heart disease, stroke) complications of DM. Achieving and maintaining glucose concentrations as near to normal as possible by tight glycemic control is absolutely essential for the delay and/or prevention of diabetic complications, as well as for improving the length and quality of life of diabetic patients.[38,115,116]

Weight reduction with calorie-restricted diets and increased physical activity are the first-line therapy of DM.[117] This will help to control insulin resistance and reduce the metabolic risk factors. This nonpharmacological approach is reported to be affective in only 20% of the patients with type 2 diabetes.[118] If life style changes involving the diet and exercise are not sufficient to keep blood glucose levels within the normal range, oral antidiabetic medications are tried next. Lifestyle changes delay the need for combined therapy and insulin injection, which presents a considerable risk of side effects in these patients.[119,120]

Since the two recent important large-scale research studies, the Diabetes Control and Complications Trial (DCCT) study and the UK Prospective Diabetes Study (UKPDS), showed conclusively that good glycemic control can delay or prevent microvascular complications, retinopathy, renal failure, and neuropathy, the following therapeutic goals for glycemic control set by the American Diabetes Association (ADA) have been widely accepted.[121,122] These include a target of 7% for the HbA; 80 to 120 mg/dl (4.4-6.6 mmol/l) for the fasting plasma glucose; and 100 to 180 mg/dl (5.5-10 mmol/l) for a postprandial glucose.[123-125]

HbA1C is a measure of blood glucose control that provides information about average glucose levels over the previous two months.[126,127] The process of conversion from hemoglobin A to hemoglobin A1c depends on the blood glucose concentration. It provides a much better indication of glycemic control than blood or urinary glucose levels.[128] Effective treatment will prevent the development of microvascular complications and risk of CVDs, which are the leading cause of death in diabetic patients.[123,129] Strong correlation between obesity and the risk of diabetes development, and the contribution of excessive body fat to glucose intolerance are among the factors that underline the importance of diet and exercise in the treatment of diabetes.[130] The effect of diet and/or exercise on the regulation of blood glucose in diabetic patients has been shown in several small- and large-scale studies. Lower socioeconomic status and limited access to healthcare are among the factors that significantly contribute to the higher incidence of diabetes complications.

The hypothesis of glucose toxicity states that hyperglycemia impairs both insulin secretion and sensitivity, shifting superfluous glucose from the normal glycolytic pathway to the minor sorbitol, hexosamine, and glycation pathways. The accumulated end products of these pathways cause oxidative stress and inflammation in cells and blood vessel walls, resulting in pancreatic β-cell dysfunction and systemic atherosclerosis.[2]

Recently, longer follow-up of the DCCT and UKPDS participants found that despite a loss of the difference in HbA1c levels after the trial, myocardial infarction was reduced by 15% among nonobese patients given sulfonylurea and insulin and by 33% among obese patients given metformin; all-cause mortality was also reduced in this group.[119,131]

Similarly, the recent Action to Control Cardiovascular Risk in Diabetes trial, which achieved an average HbA1c of 6.4% in the treatment arm *vs* 7.5% in the control arm, found a 24% reduction in the hazard of nonfatal myocardial infarction, albeit that this trial was stopped prematurely because of increased all-cause and overall cardiovascular mortality in the intensive glycemic control group.[41,132]

Research studies have shown that control of blood glucose, blood pressure, and blood lipid levels helps prevent complications in people with type 1 or type 2 diabetes.[42]

Hypertension management

Blood pressure management is a key element in the management in most patients with diabetes, particularly those who are elderly. Currently, the ADA recommends a blood pressure of <130/80 mmHg to minimize cardiovascular, renal, and other complications.[133] A recent study, the Hypertension in the Very Elderly Trial, showed that blood pressure control to <150/80 mmHg in patients >80 years of age (treated with the diuretic indapamide, or the angiotensin-converting enzyme (ACE) inhibitor perindopril) led to a reduction of the risk of fatal or nonfatal stroke by 30%, a 39% reduction in the rate of death from stroke (95% CI, 1-62; $P = 0.05$), a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from cardiovascular causes, and a 64% reduction in the rate of heart failure. Although not defined as a diabetic population, 11.8% of the study groups had CVD.[40,44]

Lipid management

Treatment of cholesterol disorders with HMG CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase) inhibitors, or "statins," reduces the risk of first major coronary event by ~25%.[99,100] The ADA recommends treatment of total cholesterol to <200 mg/dl, triglycerides to <150 mg/dl, HDL (High-density lipoprotein) cholesterol to >40 mg/dl for men and >50 mg/dl for women, and LDL (Low-density lipoprotein) cholesterol to <100 mg/dl to reduce the risk of cardiovascular events in people with diabetes.[134] Evidence also shows that atorvastatin and simvastatin reduce the risk in type 2 diabetic patients regardless of their initial baseline DL (Down-low) level.[42-44] A target LDL level of <70 mg/dl may be considered for high-risk individuals.[44,135,136]

Prevention of Complications

Glycemic control has long been the mainstay for preventing progression of these complications; however, such control is not easily achieved. Alternative adjunctive approaches to treating and preventing tissue damage are being undertaken by targeting the molecular pathogenesis of diabetic complications.[2] There are specific pathogenic mechanisms of complications for which clinical therapies have been developed, including the polyol pathway, AGEPs, PKC, vascular epithelium growth factor, and the superoxide pathway.[6,137]

Aldose reductase inhibitors

It has been hypothesized[6,138] that the excessive accumulation of sorbitol is linked to certain long-term complications. Thus, AR (aldose reductase) has long been recognized as an important target for preventing the onset or progression of these complications. Although the exact mechanism is unknown, AR appear to be possible link between increased polyol pathway activity and the development of some diabetic complications; therefore, in recent years, preventive or therapeutic approaches for diabetic complications based on the polyol pathway theory have been focused on the development of potent AR inhibitors.[83,138]

In the 1980s, sorbinil became the first ARI to undergo clinical trials after promising preclinical results. Results from several studies on neuropathy, retinopathy, and nephropathy were mixed, but the majority suggested a lack of significant effects.[139-141] Hypersensitivity reactions, occurring at increased doses, further limited the agent's effectiveness. Subsequent clinical evaluations of ARIs such as tolrestat or lidorestat were halted due to toxicities before their efficacy could be definitively evaluated.[139,140] Others, such as ponalrestat and zopolrestat, were ineffective despite having more favorable side-effect profiles.[83] Zenarestat improved nerve conduction velocity and nerve morphology in a rigorous, year-long randomized, placebo-controlled trial.[139] However, further Phase 3 studies were eventually halted due to significant creatinine elevations in study participants. Epalrestat was the first successful ARI to be developed and was approved for use in Japan in 1992 for treatment of diabetic peripheral neuropathy.[108]

Two new ARIs, fidarestat and ranirestat, have more recently been evaluated in safety and efficacy studies in randomized, double-blinded, placebo-controlled trial in US and Japan, in which 279 diabetics were studied.[139] In 2004, Phase 2 trials were halted despite the positive results due to corporate restructuring of the trial sponsor. Whether evaluation of fidarestat will be resumed is unclear. Ranirestat effectively penetrates peripheral nerves and has shown encouraging effects on peripheral neuropathy at both 5 and 20 mg doses in a 12-week, double-blinded, placebo-controlled trial.[108]

Inhibitors of advanced glycation end products

Formation of AGEPs is a consequence of altered carbohydrate, fat, and protein metabolism in diabetics. The body has mechanisms to protect against glycation and AGEs such as the liver enzyme, α–keto-glutaraldehyde dehydrogenase capable of inactivating 3-DG and preventing AGE formation.[142] A variety of plasma amines may react with sugar and Amadori carbonyl groups to reduce AGEs.[100] Antioxidants can protect against glycation-derived free radicals, whereas transport proteins, for example, ceruloplasmin can bind transition metals such as cupric ions, preventing them from participating in autoxidative glycation or glycoxidation reactions.

Aminoguanidine, the first targeted AGEP therapy, is a hydrazine derivative that prevents AGEP formation by blocking carbonyl groups on Amadori products, although it is now known to react with carbonyl groups from reducing sugars or 3-DG.[99,100] These compounds include N-phenacylthiazolium bromide (PTB) and alagebrium chloride (ALT-711) which can cleave AGE-cross-links by a mechanism which is still unclear. PTB has been used to cleave AGE cross-links between albumin and collagen *in vitro*.[100] Polyamines, spermine and spermidine, have potent antiglycation effects.[143]

Antioxidants protect against glycation-derived free radicals and may have therapeutic potential.[144] Vitamin E (800 mg/day) has been shown to reduce levels of glycated hemoglobin and accumulation of AGEs in the arterial walls of diabetic patients.[145,146]

In additional studies, AGEPs have been evaluated in diabetes, hypertension, and lipid modulation. Epalrestat has been shown to reduce serum AGEPs in diabetics after 2 to 3 months of use.[147] AGEP modulation by metformin was compared with insulin, sulfonylureas (urea derivatives), or insulin plus sulfonylureas in type 2 diabetics with similar glycemic control and no renal impairment.[6,99,148]

Simvastatin treatment and adherence to an American Heart Association diet for 4 months also has been shown to decrease

cellular RAGE (receptor for advanced glycation end products) in carotid plaques of type 2 diabetics, independent of glycemic control *vs* dietary modifications alone.[4] None of these studies specifically evaluated microvascular indices, and further clinical trials are needed to confirm potential outcome benefits.

Protein kinase C inhibitors

PKC412, while not exclusively a PKC inhibitor, was the first PKC inhibitory agent to undergo clinical evaluation in a randomized, double-blinded, placebo-controlled trial.[149] Although effective in treating DME, further studies of PCK412 were abandoned due to hepatotoxicity. Ruboxistaurin is a selective PKC-β inhibitor that has been shown to improve retinal circulation parameters and decrease DME retinal leakage without significant adverse effects.[32] Ruboxistaurin is currently pending FDA approval for the treatment of DME.

Vascular endothelial growth factor inhibitors

Cediranib (RECENTIN) is a highly potent inhibitor of all three VEGFRs (VEGFR-1, -2, and -3) with a pharmacokinetic profile that is suitable for continuous once-daily oral dosing.[150] Bevacizumab is a humanized recombinant monoclonal antibody binding to VEGF prior to its attachment to the natural endothelial receptors VEGFR-1 and VEGFR-2.[150,151] SU 5416 was the first VEGFR tyrosine kinase inhibitor to be tested clinically. This compound was administered intravenously and had to be dissolved in cremophor, yielding anaphylactic reactions in a number of patients. However, the clinical development of this compound has already been stopped.[151]

Antioxidant therapy and reactive oxygen species

Vitamin E and other antioxidants act primarily to nonenzymatically scavenge certain end-product ROS, thereby limiting their effects to only a portion of the damaging end-product.[146] Currently used agents for diabetic microvascular control, including thiazolinediones, ACE inhibitors, angiotensin receptor blockers, and statins, are believed to derive some of their benefit from modulating superoxides.[28,152] To improve the effect of antioxidant therapy, compounds are being studied that specifically act against superoxide and prevent induction of the various pathogenic mechanisms. α-lipoic acid is one such compound that has received the most attention in clinical trials, which indicated that it can reduce markers of oxidation in poorly controlled diabetics and in patients with metabolic syndrome[153] [Table 2].

Table 2: Treatment of diabetic complications based on pathogenetic mechanisms

Abnormality	Compound
Polyol pathway↑	**Aldose reductase inhibitors** Sorbinil Tolrestat Ponalrestat Zopolrestat Zenarestat Lidorestat Fidarstat AS-3201 Epalrestat
Myo-Inositol↓	Myo-Inositol
Oxidative stress↑	Lipoic acid, Nutrinerve
Nerve hypoxia↑	**Vasodilators** ACE inhibitors Prostaglandin analogs
Protein kinase C↑	PKC β inhibitor
C-peptide↓	C-peptide
Neurotrophism↓	Nerve growth factor (NGF) BDNF
LCFA metabolism↓	Acetyl-L-carnitine
GLA synthesis↓	γ-Linolenic acid (GLA)
NEG↑	Aminoguanidine

↑- Increase; ↓- Decrease; BDNF, brain-derived neurotrophic factor; NEG, non-enzymatic glycation; LCFA, long-chain fatty acids; NBF, nerve blood flow

Conclusion

Targets are not being met and drugs are not being prescribed appropriately in most patients with diabetes worldwide. Patients find it difficult to comply with lifestyle advice, attendance for screening, and drugs and those with most difficulty have worse outcomes. Many changes are needed to prevent the complications of diabetes and minimize their impact. Many examples of novel ways of improving outcomes exist.

Significant advances have occurred in all aspects of diabetes over the past 12 months. The most dramatic have involved concepts relating to etiology of type 1 and type 2 and diabetes complications. Both forms of diabetes and its complications remain among the most misunderstood and mismanaged of conditions, and it is to be hoped that current discussion about who should manage these conditions will focus attention on desirable standards of care.

Acknowledgements

The authors thank Dr. Deepti Jain and Mr. C. Karthikeyan from RGTU, Bhopal, for their valuable suggestions in carrying out this research work. The authors are also thankful to Prof. Surendra K. Jain for his kind guidance.

References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4-14.
2. Available from: http://www.who.int/diabetes/en/. [accessed in 2010 May].
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
4. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, *et al*. Diabetes in Asia: Epidemiology, risk factors, and pathophysiology. JAMA 2009;301:2129-40.
5. Allen KV, Frier BM, Strachan MW. The relationship between type 2 diabetes and cognitive dysfunction: Longitudinal studies and their methodological limitations. Eur J Pharmacol 2004;490:169-75.
6. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, *et al*. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: The Third National Health and Nutrition Examination Survey (1988-1994). Diabetes Care 1998;21:518-24.
7. Sweileh WM, Sawalha AF, Zyoud SH, Al-Jabi SW, Tameem EJ, Shraim NY. Evaluation of antihypertensive therapy in diabetic hypertensive patients: Impact of ischemic heart disease. Pharma Pract (Internet) 2009;7:40-6.
8. Craig LC, Stitzel RE. Modern pharmacology with clinical applications. 5th ed. Boston: Little, Brown; 1997;763-76.

9. Heydari I, Radi V, Razmjou S, Amiri A, Chronic complications of diabetes mellitus in newly diagnosed patients. Int J Diabetes Mellitus 2010;2:61-3.
10. Chakrabarti S, Khan ZA, Cukiernik M, Fukuda G, Chen S, Mukherjee S. Alteration of endothelins: A common pathogenetic mechanism in chronic diabetic complications. Int J Exp Diab Res 2002;3:217-31.
11. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabet 2008;26:357.
12. Tripathi KD. Essentials of medical pharmacology. 5th ed. New Delhi: Jaypee Brothers; 2005.
13. Hardman JG, Limbird LE, Gilman AG. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York: McGraw-Hill; 2001. ISBN 0-07-135469-7.
14. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. Lancet 2010;375:408-18.
15. Reinauer H, Home PD, Kanagasabapathy AS, Heuck CC, Laboratory diagnosis and monitoring of diabetes mellitus. Geneva: World Health Organization; 2002. p. 1-26.
16. Stolar M. Glycemic control and complications in type 2 diabetes mellitus. Am J Med 2010;123:S3-11.
17. Schwartz SS. Pioglitazone for the treatment of type 2 diabetes in patients inadequately controlled on insulin. Diabetes Metab Syndr Obes 2010;3:243-52.
18. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ 2000;321:405-12.
19. Singh R, Ramasamy K, Abraham C, Gupta V, Gupta A. Diabetic retinopathy: An update. Indian J Ophthalmol 2008;56:179-88.
20. Leiter LA. The prevention of diabetic microvascular complications of diabetes: Is there a role for lipid lowering?. Diabetes Res Clin Pract 2005;68S2:S3-14.
21. Buraczynska M, Ksiazek P, Baranowicz-Gaszczyk I, Jozwiak L. Association of the VEGF gene polymorphism with diabetic retinopathy in type 2 diabetes patients. Nephrol Dial Transplant 2007;22:827-32.
22. Cunha-Vaz J, Coimbra, Portugal. Effect of candesartan on diabetic retinopathy (the DIRECT studies). Int Diabetes Monitor 2009;21:204-5.
23. Sopharak A, Uyyanonvara B, Barman S. Automatic exudate detection from non-dilated diabetic retinopathy retinal images using fuzzy C-means clustering. Sensors 2009;9:2148-61.
24. Alibrahim E, Donaghue KC, Rogers S, Hing S, Jenkins AJ, Chan A, *et al*. Retinal vascular caliber and risk of retinopathy in young patients with type 1 diabetes. Ophthalmology 2006;113:1499-503.
25. Sankaranarayanan K, Chakraborty R, Boerwinkle EA. Ionizing radiation and genetic risks VI. Chronic multifactorial diseases: A review of epidemiological and genetical aspects of coronary heart disease, essential hypertension and diabetes mellitus. Mutat Res 1999;436:21-57.
26. Kaiser RS, Maguire MG, Grunwald JE. One-year outcomes of panretinal photocoagulation in proliferative diabetic retinopathy. Am J Ophthalmol 2000;129:178-85.
27. Ritz E, Stefanski A. Diabetic nephropathy in type II diabetes. Am J Kidney Dis 1996;27:167-94.
28. Klein R, Kobrin Klein BE. The epidemiology of eye disease: From glycemia to genetics. Investig Ophthalmol Visual Sci 2006;47:1747-53.
29. Aiello LM. Perspectives on diabetic retinopathy. Perspective 2003;136:122-35.
30. Yu BP, Chung HY. Oxidative stress and vascular aging. Diabetes Res Clin Pract 2001;54:S73-80.
31. Foggensteiner L, Mulroy S, Firth J. Management of diabetic nephropathy. J Royal Soc Med 2001;94:210-7.
32. Xu J, Lee ET, Best LG, Lee ET, Begum M, Knowler WC. Association of albuminuria with all- cause and cardiovascular disease mortality in diabetes: The Strong Heart study. Br J Diabetes Vasc Dis 2005;5:334-40.
33. Feldman EL. Oxidative stress and diabetic neuropathy: A new understanding of an old problem. J Clin Investig 2003;111:1-3.
34. Hall PM. Prevention of progression in diabetic nephropathy. Diabetes Spect 2006;19:18-24.
35. Brantsma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT; PREVEND Study Group. Cardiovascular and renal outcome in subjects with K/DOQI stage 1-3 chronic kidney disease: The importance of urinary albumin excretion. Nephrol Dial Transplant 2008;23:3851-8.
36. Isharwal S, Misra A, Wasir JS, Nigam P. Diet and insulin resistance: A review and Asian Indian perspective. Indian J Med Res 2009;129:485-99.
37. Jafar TH, Chaturvedi N, Pappas G. Prevalence of overweight and obesity and their association with hypertension and diabetes mellitus in an Indo- Asian population. CMAJ 2006;175:1071-7.
38. Lewis EJ, Xu X. Abnormal glomerular permeability characteristics in diabetic nephropathy. Diabetes Care 2008;31:S202-7.
39. Cooper ME, Gilbert RE, Epstein M. Pathophysiology of diabetic nephropathy. Metabolism 1998;47:3-6.
40. Edwards JR, Prozialeck WC. Cadmium, diabetes and chronic kidney disease. Toxicol Appl Pharmacol 2009;238:289-93.
41. Bretzel RG. Prevention and slowing down the progression of the dialkic nephropathy through antihypertensive therapy. J Diabetes Compl 1997;11:112-22.
42. Muragundla A, Chopra K. Quercetin: An anti-oxidant bioflavonoid, attenuates diabetic nephropathy in rats. Clin Exp Pharmacol Physiol 2004;31:244-8.
43. United Kingdom Prospective Diabetic Study Group. Intense blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
44. Abdel-Zaher AO, Abdel-Rahman MM, Hafez MM, Omran FM. Role of nitric oxide and reduced glutathione in the protective effects of aminoguanidine, gadolinium chloride and oleanolic acid against acetaminophen- induced hepatic and renal damage. Toxicology 2007;234:124-34.
45. Adler S, Nast C. Diabetic nephropathy: Pathogenesis and treatment. Ann Rev Med 1993;44:303-15.
46. Greene DA, Sima AA. Diabetic neuropathy. Ann Rev Med 1990;41:303-17.
47. Kärvestedt L, Mårtensson E, Grill V, Elofsson S, von Wendt G, Hamsten A, *et al*. The prevalence of peripheral neuropathy in a population-based study of patients with type 2 diabetes in Sweden. J Diabetes Compllications 2011;25:97-106.
48. Cameron NE. The aetiology of neuropathy in experimental diabetes. Br J Diabetes Vasc Dis 2003;3:98-105.
49. Badawi A, Klip A, Haddad P, Cole DE, Bailo BG, El-Sohemy A, *et al*. Type 2 diabetes mellitus and inflammation: Prospects for biomarkers of risk and nutritional intervention. Diabetes Metab Syn Obesit Targets Ther 2010;3:173-86.
50. Yusuf O, Nuray AV, Nuray AR. Diabetic complications in experimental models. Tr J Med Sci 1998;22:331-41.
51. Mohora M, Greabu M, Muscurel C. The sources and the targets of oxidative stress in the etiology of diabetic complications. Romanian J Biophys 2007;17:63-84.
52. Vinik AI, Strotmeyer ES, Nakave AA. Diabetic neuropathy in older adults. Clin Geriatr Med 2008;24:407.
53. Limaye PV, Raghuram N, Sivakami S. Oxidative stress and gene expression of antioxidant enzymes in the renal cortex of streptozotocininduced diabetic rats. Mole Cell Biochem 2003;243:147-52.
54. Valensi P, Giroux C, Seeboth-Ghalayini B, Atali JR. Diabetic peripheral neuropathy: Effects of age, duration of diabetes, glycemic control, and vascular factors. J Diabetes Compl 1997;11:27-34.
55. Schemmel KE, Padiyara RS, D'Souza JJ. Aldose reductase inhibitors in the treatment of diabetic peripheral neuropathy: A review. J Diabetes Complications 2010;24:354-60.
56. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM.. Diabetic somatic neuropathies. Diabetes Care 2004;27:1458-86.
57. Hatzitolios AI, Didangelos TP, Zantidis AT, Tziomalos K, Giannakoulas GA, Karamitsos DT. Diabetes mellitus and cerebrovascular disease: Which are the actual data? J Diabetes Complications 2009;23:283-96.
58. Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Effect of intensive diabetes treatment on carotid artery wall thickness in the epidemiology of diabetes interventions and complications. Diabetes 1999;48:383-90.
59. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet 2009;374:934-47.

60. Pandhi N, Smith MA, Kind AJ, Frytak JR, Finch MD. The quality of diabetes care following hospitalization for ischemic stroke. Cerebrovasc Dis 2009;27:235-40.
61. Russell NE, Foley M, Kinsley BT, Firth RG, Coffey M, McAuliffe FM. Effect of pregestational diabetes mellitus on fetal cardiac function and structure. Am J Obstet Gynecol 2008;199:312.e1-7.
62. Karnib HH, Ziyadeh FN. The cardiorenal syndrome in diabetes mellitus. Diabetes Res Clin Pract 2010;89:201-8.
63. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: Epidemiology pathophysiology and management. JAMA 2002;287:2570-81.
64. Giles TD. The patient with diabetes mellitus and heart failure: At-risk issues. Am J Med 2003;115:107S-10.
65. Hunt KJ, Williams K, Resendez RG, Hazuda HP, Haffner SM, Stern MP. All-cause and cardiovascular mortality among diabetic participants in the San Antonio heart study. Diabetes Care 2002;26:1557-63.
66. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Prob Cardiol 2010;35:72-115.
67. Type 2 Diabetes practical targets and treatments. 4th ed. and *In vivo* Communications (Asia) Pvt Limited, Singapore, on behalf of the Asian-Pacific Type 2 Diabetes Policy Group and International Diabetes Federation (IDF) Western Pacific Region; Australia: International Diabetes Institute (IDI), Melbourne; 2005.2005.
68. Shakil M, Ahmed ST, Samiullah S, Perveen K, Sheikh S, Humaira A. Influence of hypertension and diabetes mellitus on senile cataract. Pak J Physiol 2008;4(2):30-3.
69. Zanella MT, Kohlmann O Jr, Ribeiro AB. Treatment of obesity hypertension and diabetes syndrome. Hypertension 2001;38:705-8.
70. Kagawa E, Inoue I, Kawagoe T. History of diabetes mellitus as a neurologic predictor in comatose survivors of cardiac arrest of cardiac origin treated with mild hypothermia. Resuscitation 2009;80:881-7.
71. Harman-Boehm I, Sosna T, Lund-Andersen H. The eyes in diabetes and diabetes through the eyes. Diabetes Res Clin Pract 2007;78S:S51-8.
72. Tahrani AA, Piya MK, Kennedy A, Barnett AH. Glycaemic control in type 2 diabetes: Targets and new therapies. Pharmacol Ther 2010;125:328-61.
73. Koya D, Jirousek MR, Lin YW, Ishii H, Kuboki K, King GL. Characterization of protein kinase C isoform activation on the gene expression of transforming growth factor β, extracellular matrix components, and prostanoids in the glomeruli of diabetic rats. J Clin Invest 1997;100:115-26.
74. King GL, Loeken MR. Hyperglycemia-induced oxidative stress in diabetic complications. Histochem Cell Biol 2004;122:333-8.
75. Duarte AI, Proença T, Oliveira CR, Santos MS, Rego AC. Insulin Restores Metabolic Function in Cultured Cortical Neurons Subjected to Oxidative Stress. Diabetes 2006;55:2863-70.
76. Park JS, Ahn CW. Educational program for diabetic patients in Korea—Multidisplinary intensive management. Diabetes Res Clin Pract 2007;77:S194-8.
77. Brown LC, Johnson JA, Majumdar SR, Tsuyuki RT, McAlister FA. Evidence of suboptimal management of cardiovascular risk in patients with type 2 diabetes mellitus and symptomatic atherosclerosis. CMAJ 2004;171:1189-92.
78. Yamashita T, Mimura K, Umeda F, Kobayashi K, Hashimoto T, Nawata H. Increased Transendothelial Permeation of Albumin by High Glucose Concentration. Metabolism 1995;144:739-44.
79. Flegel K. Controlling the complications of diabetes: It's about the sugar. CMAJ 2009;15:357.
80. Berrone E, Beltramo E, Solimine C, Ape AU, Porta M. Regulation of Intracellular Glucose and Polyol Pathway by Thiamine and Benfotiamine in Vascular Cells Cultured in High Glucose. J Biol Chem 2006;281:9307-13.
81. Hothersall JS, Taylaur CE, McLean P. Antioxidant Status in an *in vitro* Model for Hyperglycemic Lens Cataract Formation: Effect of Aldose Reductase Inhibitor Statil. Biochem Med Metab Biol 1988;40:109-17.
82. Horie S, Nagai H, Yuuki T, Narita Y, Tsuda Y, Nakajima T, *et al*. Effect of SG-210, a Novel Aldose Reductase Inhibitor, on Impaired Polyol Pathway in Rats Received Diabetic Manipulations. J Diabetes Complications 1998;12:163-9.
83. Hotta N. New approaches for treatment in diabetes: Aldose reductase inhibitors. Biomed Pharmocother 1995;5:232-43.
84. Van Zandt MC, Sibley EO, McCann EE, Combs KJ, Flam B, Sawicki DR, *et al*. Design and synthesis of highly potent and selective (2-arylcarbamoyl-phenoxy)-acetic acid inhibitors of aldose reductase for treatment of chronic diabetic complications. Bioorg Med Chem 2004;12:5661-75.
85. Ng DP, Conn J, Chung SS, Larkins RG. Aldose reductase (AC)*n* microsatellite polymorphism and diabetic microvascular complications in Caucasian Type 1 diabetes mellitus. Diabetes Res Clin Pract 2001;52:21-7.
86. Forbes JM, Coughlan MT, Cooper ME. Oxidative Stress as a Major Culprit in Kidney Disease in Diabetes. Diabetes 2008;57:1446-54.
87. Pricci F, Leto G, Amadio L, Iacobini C, Cordone S, Catalano S, *et al*. Oxidative stress in diabetes- induced endothelial dysfunction involvement of nitric oxide and protein kinase c. Free Radic Biol Med 2003;35:683-94.
88. Mokini Z, Marcovecchio ML, Chiarelli F.. Molecular pathology of oxidative stress in diabetic angiopathy: Role of mitochondrial and cellular pathways. Diabetes Res Clin Pract 2010;87:313-21.
89. Taniyama Y, Griendling KK. Reactive Oxygen Species in the Vasculature: Molecular and Cellular Mechanisms. Hypertension 2003;42:1075-81.
90. Boel E, Selmer J, Flodgaard HJ, Jensen T. Diabetic Late Complications: Will Aldose Reductase Inhibitors or Inhibitors of Advanced Glycosylation Endproduct Formation Hold Promise? J Diabetes Complications 1995;9:104-29.
91. Mehta JL, Rasouli N, Sinha AK, Molavi B. Oxidative stress in diabetes: A mechanistic overview of its effects on atherogenesis and myocardial dysfunction. Int J Biochem Cell Biol 2006;38:794-803.
92. Yim MB, Yim HS, Lee C, Kang SO, Chock PB. Protein Glycation Creation of Catalytic Sites for Free Radical Generation. Ann N Y Acad Sci 2001;928:48-53.
93. Fukunaga-Takenaka R, Shirai Y, Yagi K, Adachi N, Sakai N, Merino E, *et al*. Importance of chroman ring and tyrosine phosphorylation in the subtype-specific translocation and activation of diacylglycerol kinase α by D-α-tocopherol. Genes Cells 2005;10:311-9.
94. Meier M, Menne J, Park JK, Haller H. Nailing down PKC isoform specificity in diabetic nephropathy—two's company, three's a crowd. Nephrol Dial Transplant 2007;22:2421-25.
95. Chu S, Bohlen HG. High concentration of glucose inhibits glomerular endothelial eNOS through a PKC mechanism. Am J Physiol Renal Physiol 2004;287:F384-92.
96. Danielsen AG, Liu F, Hosomi Y, Shii K, Roth RA. Activation of Protein Kinase Ca Inhibits Signaling by Members of the Insulin Receptor Family. J Biol Chem 1995;270:21600-5.
97. Maritim AC, Sanders RA, Watkins JB 3rd. Diabetes, Oxidative Stress, and Antioxidants: A Review. J Biochem Mol Toxicol 2003;17:24-38.
98. Sensi M, Pricci F, Pugliese G, De Rossi MG, Petrucci AF, Cristina A, *et al*. Role of advanced glycation end-products (AGE) in late diabetic complications. Diabetes Res Clin Pract 1995;28:9-17.
99. Huebschmann AG, Regensteiner JG, Vlassara H, Reusch JE. Diabetes and Advanced Glycoxidation End Products. Diabetes Care 2006;29:1420-32.
100. Wolf G. New insights into the pathophysiology of diabetic nephropathy: From haemodynamics to molecular pathology. Eur J Clin Invest 2004;34:785-96.
101. Brownlee M. The Pathobiology of Diabetic Complications A Unifying Mechanism. Diabetes 2005;54:1615-25.
102. Dandona P, Chaudhuri A, Mohanty P. Macronutrients, Advanced Glycation End Products, and Vascular Reactivity. Diabetes Care 2007;30:2750-1.
103. Sato E, Mori F, Igarashi S. Corneal advanced glycation end products increase in patients with proliferative diabetic retinopathy. Diabetes care 2001;24:479-82.
104. Jakuš V, Rietbrock N. Advanced Glycation End-Products and the Progress of Diabetic Vascular Complications. Physiol Res 2004;53:131-42.
105. Yamagishi S, Ueda S, Okuda S. A possible involvement of crosstalk between advanced glycation end products (AGEs) and asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor in accelerated atherosclerosis in diabetes. Med Hypotheses 2007;69:922-4.
106. Fadini GP, Sartore S, Agostini C, Avogaro A. Significance of Endothelial Progenitor Cells in Subjects With Diabetes. Diabetes Care

2007;30:1305-13.
107. Bansal V, Kalita J, Misra UK. Diabetic neuropathy. Postgrad Med J 2006;82;95-100.
108. Sherril S. Pathophysiology of Diabetic Nephropathy. Nephrol Nurs J 2007;34:631-3.
109. Mezquita J, Mezquita B, Pau M, Mezquita C. Characterization of a Novel Form of Angiopoietin-2 (Ang- 2B) and Expression of VEGF and Angiopoietin-2 during Chicken Testicular Development and Regression. Biochem Biophys Res Communi 1999;260:492-8.
110. Klöpper J, Lindenmaier W, Fiedler U, Mehlhorn A, Stark GB, Finkenzeller G, *et al*. High efficient adenoviral-mediated VEGF and Ang-1 gene delivery into osteogenically differentiated human mesenchymal stem cells. Microvasc Res 2008;75:83-90.
111. Economidou F, Antoniou KM, Tzanakis N, Sfiridaki K, Siafakas NM, Schiza SE. Angiogenic molecule Tie-2 and VEGF in the pathogenesis of pleural effusions. Respir Med 2008;102:774-9.
112. Amiri F, Shaw S, Wang X, Tang J, Waller JL, Eaton DC, *et al*. Angiotensin II activation of the JAK/STAT pathway in mesangial cells is altered by high glucose. Kidney Int 2002;61:1605-16.
113. Pang Y, Bounelis P, Chatham JC, Marchase RB. Hexosamine Pathway Is Responsible for Inhibition by Diabetes of Phenylephrine-Induced Inotropy. Diabetes 2004;53:1074-81.
114. Kanji MI, Toews ML, Carper WR. Robert. A Kinetic Study of Glucose-6-phosphate Dehydrogenase. J Biol Chem 1976;251:2258-62.
115. Available from: http://www.preventdiabetes .com. [Last accessed on Apr 2010.
116. Brown AF, Mangione CM, Saliba D, Sarkisian CA, California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for Improving the Care of the Older Person with Diabetes Mellitus. J Am Geriatr Soc 2003;51:S265-80.
117. Kalra S, Kalra B, Unnikrishnan A, Agrawal N, Kumar S. Optimizing weight control in diabetes: Antidiabetic drug selection. Diabetes Metab Syndr Obes 2010;3:297-9.
118. Jenssen TG, Tonstad S, Claudi T, Midthjell K, Cooper J. The gap between guidelines and practice in the treatment of type 2 diabetes a nationwide survey in Norway. Diabetes Res Clin Pract 2008;80:314-20.
119. Molyneaux LM, Constantino MI, McGill M, Zilkens R, Yue DK. Better glycaemic control and risk reduction of diabetic complications in Type 2 diabetes: Comparison with the DCCT. Diabetes Res Clin Pract 1998;42:77-83.
120. Wijesuriya M, Williams R, Yajnik C. The Kathmandu Declaration: ''Life Circle'' approach to prevention and care of diabetes mellitus. Diabetes Res Clin Pract 2010;87:20-6.
121. Gomez-Perez FJ, Aguilar-Salinas CA, Almeda-Valdes P, Cuevas-Ramos D, Lerman Garber I, Rull JA. HbA1c for the Diagnosis of Diabetes Mellitus in a Developing Country. A Position Article. Arch Med Res 2010;41:302-8.
122. Blonde L. Current Antihyperglycemic Treatment Guidelines and Algorithms for Patients with Type 2 Diabetes Mellitus. Am J Med 2010;123:S12-8.
123. Del Cañizo-Gómez FJ, Moreira-Andrés MN. Cardiovascular risk factors in patients with type 2 diabetes Do we follow the guidelines? Diabetes Res Clin Pract 2004;65:125-33.
124. Zhang L, Krzentowski G, Albert A, Lefebvre PJ. Risk of Developing Retinopathy in Diabetes Control and Complications Trial Type 1 Diabetic Patients with Good or Poor Metabolic Control. Diabetes Care 2001;24:1275-9.
125. Motta M, Bennati E, Cardillo E, Ferlito L, Malaguarnera M. The value of glycosylated hemoglobin (HbA1c) as a predictive risk factor in the diagnosis of diabetes mellitus (DM) in the elderly. Arch Gerontol Geriatr 2010;50:60-4.
126. Yu PC, Bosnyak Z, Ceriello A. The importance of glycated haemoglobin (HbA1c) and postprandial glucose (PPG) control on cardiovascular outcomes in patients with type 2 diabetes. Diabetes Res Clin Pract 2010;89:1-9.
127. Davidson MB, Schriger DL. Effect of age and race/ethnicity on HbA1c levels in people without known diabetes mellitus: Implications for the diagnosis of diabetes. Diabetes Res Clin Pract 2010;87:415- 21.
128. Warren RE. The stepwise approach to the management of type 2 diabetes. Diabetes Res Clin Pract 2004;65S:S3-8.
129. Dokken BB. The Parodox of Glycemic Control and Cardiovascular Complications: Sorting Out the Data. Diabetes Spectr 2008;21;150-2.
130. Kilpatrick ES, Rigby AS, Atkin SL. Insulin Resistance, the Metabolic Syndrome, and Complication Risk in Type 1 Diabetes. Diabetes Care 2007;30:707-12.
131. Kushner P. Minimizing the risk of hypoglycemia in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes 2010;3:49-53.
132. Naqshbandi M, Harris SB, Esler JG, Antwi-Nsiah F. Global complication rates of type 2 diabetes in Indigenous peoples: A comprehensive review. Diabetes Res Clin Pract 2008;82:1-17.
133. Steigerwalt S. Management of Hypertension in Diabetic Patients with Chronic Kidney Disease. Diabetes Spectr 2008;21:30-6.
134. American Diabetes Association Professional Practice Committee and the Executive Committee, October 2001. Evidence-Based Nutrition Principles and Recommendations for the Treatment and Prevention of Diabetes and Related Complications. Clin Diabetes 2002;20:S50-60.
135. Huang ES, Brown SE, Ewigman BG, Foley EC, Meltzer DO. Patient Perceptions of Quality of Life with Diabetes-Related Complications and Treatments. Diabetes Care 2007;30:2478-83.
136. American Diabetes Association. Standards of medical care in diabetes-2008. Diabetes Care 2008;31:S12-54.
137. Cheng AY, Leiter LA. Cardiovascular risk and glycemic control. CMAJ 2009;180:907-8.
138. Kinoshita JH. A Thirty Year Journey in the Polyol Pathway. Exp Eye Res 1990;50:567-73.
139. Veves A. Aldose Reductase Inhibitors for the Treatment of Diabetic Neuropathy. Contemporary Diabetes: Diabetic Neuropathy: Clinical Management. 2nd ed. In: Veves A, Malik R. Totowa, NJ: Humana Press Inc; 2007. p. 309-20.
140. Yasuda H, Terada M, Maeda K, Kogawa S, Sanada M, Haneda M, *et al*. Diabetic neuropathy and nerve regeneration. Prog Neurobiol 2003;69:229-85.
141. Crabbe MJ, Goode D. Aldose reductase: A window to the treatment of diabetic complications?. Prog Retin Eye Res 1998;17: 313-83.
142. Rojas A, Morales MA. Advanced glycation and endothelial functions: A link towards vascular complications in diabetes. Life Sci 2004;76:715-30.
143. Khan KM, Khan M, Ali M, Taha M, Rasheed S, Perveen S, *et al*. Synthesis of bis-Schiff bases of isatins and their antiglycation activity. Bioorg Med Chem 2009;17:7795-801.
144. Pazdro R, Burgess JR. The role of vitamin E and oxidative stress in diabetes complications. Mech Ageing Dev 2010;131:276-86.
145. Bonnefont-Rousselot D, Bastard JP, Jaudon MC, Delattre J. Consequences of The Diabetic Status on The Oxidant/Antioxidant Balance. Diabetes Metab 2000;26:163-76.
146. van Dam PS, van Asbeck BS, Bravenboer B, van Oirschot JF, Gispen WH, Marx JJ. Nerve function and oxidative stress in diabetic and vitamin e-deficient rats. Free Radic Biol Med 1998;24:18-26.
147. Iso K, Tada H, Kuboki K, Inokuchi T. Long-term effect of epalrestat, an aldose reductase inhibitor, on the development of incipient diabetic nephropathy in Type 2 diabetic patients. J Diabetes Complications 2001;15:241-4.
148. Khan KM, Saeed S, Ali M, Gohar M, Zahid J, Khan A, *et al*. Unsymmetrically disubstituted urea derivatives: A potent class of antiglycating agents. Bioorg Med Chem 2009;17:2447-51.
149. Ha H, Kim KH. Pathogenesis of diabetic nephropathy: The role of oxidative stress and protein kinase C. Diabetes Res Clin Pract 1999;45:147-51.
150. van Cruijsen H, Voest EE, Punt CJ, Hoekman K, Witteveen PO, Meijerink MR, *et al*. Phase I evaluation of cediranib, a selective VEGFR signaling inhibitor, in combination with gefitinib in patients with advanced tumours. Eur J Cancer 2010;46:901-11. Available from: www.ejconline.com. [Last accessed on 2010].
151. Eskens FA, Verweij J. The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors; A review. Eur J Cancer 2006;42:3127-39.

152. Cighetti G, Fermo I, Aman CS, Ferraroni M, Secchi A, Fiorina P. Dimethylarginines in complicated type 1 diabetes: Roles of insulin, glucose, and oxidative stress. Free Radic Biol Med 2009;47:307-11.
153. Obrosova IG, Pacher P, Szabó C, Zsengeller Z, Hirooka H, Stevens MJ, *et al*. Aldose Reductase Inhibition Counteracts Oxidative Nitrosative Stress and Poly (ADP-Ribose) Polymerase Activation in Tissue Sites for Diabetes Complications. Diabetes 2005;54:234-42.

Cite this article as: Rambhade SK, Singh S, Goswami RB, Rambhade A. Occurrence, complications, and interventions of diabetes: A new understanding of an old problem. Syst Rev Pharm 2011;2:8-18.

Source of Support: Nil, **Conflict of Interest:** None declared.

New features on the journal's website

Optimized content for mobile and hand-held devices
HTML pages have been optimized of mobile and other hand-held devices (such as iPad, Kindle, iPod) for faster browsing speed.
Click on **[Mobile Full text]** from Table of Contents page.
This is simple HTML version for faster download on mobiles (if viewed on desktop, it will be automatically redirected to full HTML version)

E-Pub for hand-held devices
EPUB is an open e-book standard recommended by The International Digital Publishing Forum which is designed for reflowable content i.e. the text display can be optimized for a particular display device.
Click on **[EPub]** from Table of Contents page.
There are various e-Pub readers such as for Windows: Digital Editions, OS X: Calibre/Bookworm, iPhone/iPod Touch/iPad: Stanza, and Linux: Calibre/Bookworm.

E-Book for desktop
One can also see the entire issue as printed here in a 'flip book' version on desktops.
Links are available from Current Issue as well as Archives pages.
Click on View as eBook

Author Help: Online Submission of the Manuscripts

Articles can be submitted online from http://www.journalonweb.com. For online submission articles should be prepared in two files (first page file and article file). Images should be submitted separately.

1) **First Page File:**
Prepare the title page, covering letter, acknowledgement, etc., using a word processor program. All information which can reveal your identity should be here. Use text/rtf/doc/pdf files. Do not zip the files.
2) **Article file:**
The main text of the article, beginning from Abstract till References (including tables) should be in this file. Do not include any information (such as acknowledgement, your names in page headers, etc.) in this file. Use text/rtf/doc/pdf files. Do not zip the files. Limit the file size to 1 MB. Do not incorporate images in the file. If file size is large, graphs can be submitted as images separately without incorporating them in the article file to reduce the size of the file.
3) **Images:**
Submit good quality color images. Each image should be less than **4096 kb (4 MB)** in size. Size of the image can be reduced by decreasing the actual height and width of the images (keep up to about 6 inches and up to about 1200 pixels) or by reducing the quality of image. JPEG is the most suitable file format. The image quality should be good enough to judge the scientific value of the image. Always retain a good quality, high resolution image for print purpose. This high resolution image should be sent to the editorial office at the time of sending a revised article.
4) **Legends:**
Legends for the figures/images should be included at the end of the article file.