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**Diabetes Mellitus- Its complications, factors influencing complications and prevention- An Overview**

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**ABSTRACT**

*This review aims to summarize the major advances of the preceding year and to put them in to 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.*

**Key words:** Diabetes, Diabetic complications, Polyol pathway, Oxidative stress, Protein kinase c.

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**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]. J.E. 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 J.E. Shaw et al, 2030 estimate of 439 million is 20% higher than the same study's estimate for 2030. In 2005, an estimated 1.1 million people died from diabetes. Almost 80% of diabetes deaths occur in low and middle income countries. 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 towards 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.

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, 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].

### **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  $\beta$  cells are detectable in blood, but some are idiopathic (type 1B)-no  $\beta$  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  $\beta$  cell mass has been reported, though in some cases reduction in  $\beta$  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 factor from early in the disease process, including abdominal obesity, hypertension, dyslipidaemia, 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 diabetic retinopathy (DR) are 25 times more likely to become blind than non-diabetics[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].

Diabetic retinopathy 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].

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

The final metabolic pathway causing DR is unknown. There are several theories. Electrolytic imbalance caused by the high aldose reductase 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 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, non-perfusion, 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 diabetic retinopathy (PDR)[28,29]. VEGFs are released by retinal pigment epithelium, pericytes and endothelial cells of the retina[30].

### **Nephropathy**

Diabetes is among leading causes of kidney failure. 10-20% 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]. While 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 microalbuminuria 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[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 arteriosclerosis and glomerulosclerosis with obliteration of the filtration area due to increased production and decreased degradation of extracellular matrix (ECM) proteins. In the later stages, patients develop characteristic nodular accumulation of extracellular matrix 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.

Identification of patients at high risk by screening for microalbuminuria now occurs in many hospital clinics and potentially early and effective anti-hypertensive treatment in these patients can postpone or prevent clinical nephropathy. Blockade of the renin-angiotensin system by angiotensin I converting enzyme inhibitors may decrease microalbuminuria in normotensive diabetic patients independently of the fall in blood pressure[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. Neuropathic pain can be described as a sensation of paresthesia, numbness, and burning that is caused by the sustained, abnormal processing of CNS neuronal input. 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 [49], though it has not been studied in age related neuropathies. P and E-selectin, activated during the inflammatory process, predict the decline in peripheral nerve function among diabetic patients. 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[52]. Oxidative and nitrosative stress and inflammation are implicated in several neurodegenerative disorders including Alzheimer's disease and amyotrophic lateral sclerosis (ALS). It is greater in diabetic patients prior to development of peripheral neuropathy and particularly in those with peripheral neuropathy [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].

To date, pharmacologic agents used in the treatment of diabetic neuropathy are used empirically to address symptoms are 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 [55,56].

### **Cardiomyopathy**

Diabetes increases the risk of heart disease and stroke and nearly 50% of people with diabetes die of cardiovascular disease. 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 diabetes mellitus (DM), and cardiovascular disease, including stroke [57,58]. DM, hypertension, smoking, dyslipidemia, atrial fibrillation (AF), 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 [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 [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:

Increased production of free oxygen radicals and oxidative stress [71].

Increased production of glycosylated products [72].

Increased activity of aldose reductase in the polyol pathway, leading to intracellular accumulation of sorbitol and fructose [71].

Activation of specific protein kinase C (PKC) isoforms [73,74].

Formation of reactive oxygen species 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  $\beta$  and PKC  $\delta$ , leads to cell proliferation,

impaired glucose and lipid metabolism, expression of atherosclerosis-promoting genes, decreased vasodilation, and increased vascular permeability.

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

Initiate insulin therapy when plasma glucose is >140-180 mg/dl.

Therapeutic target: plasma glucose 80-140 mg/dl.

The recommendations on acute stroke are the following:

Critically ill patients: plasma glucose close to 110 mg/dl and always <180 mg/dl.

Non-critically ill patients: plasma glucose 90-130 mg/dl and postprandial plasma glucose <180 mg/dl.

### **Macroangiopathy**

Clinical manifestations of atherosclerosis occur primarily in 3 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 [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].

### **Factors influencing diabetic complications**

Diabetic complications arise primarily because of hyperglycemia-induced metabolic changes leading to changes in the structural and functional properties of macro- molecules [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, protein kinase C (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 [80].

### **Polyol pathway**

The polyol pathway reduces toxic aldehydes generated by reactive oxygen species (ROS) to inactive alcohols [81]. Aldose reductase (AR), via 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 reductase activity, which reduces glutathione (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 [83].

Aldose reductase 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 and oxidative stress**

Diabetes mellitus 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. NO is a potent vasodilator formed from L-arginine by NO synthase (NOS) [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 via efflux, and dephosphorylation of myosin light chains. Endothelial dysfunction is characterized by the imbalance between contracting and relaxing factors.

A disturbance in the cellular redox balance is assumed to interfere with the proper maintenance of cellular homeostasis. 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. 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 [92].

### **PKC activation**

Protein kinase C 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.

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 extracellular matrix, 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.

Research in to novel therapeutic agents for diabetic kidney disease (DKD) focused early on PKC because hyperglycemia, the defining feature of diabetes, increases diacylglycerol, advanced glycation end products, 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 [96].

**Advanced glycation end products**

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. Over a dozen AGEPs have been detected in tissues and can be divided into three categories: [100]

Fluorescent cross-linking AGEPs such as pentosidine and crossline.

Non-fluorescent cross-linking AGEPs such as imidazolium dilysine cross-links, alkyl formyl glycosyl pyrrole (AFGP) cross-links and arginine– lysine imidazole (ALI) cross-links.

Non-cross-linking AGEPs such as pyrraline and N-carboxymethyllysine (CML).

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. AGEPs alter intracellular and extracellular proteins and their functions [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 complication [103]. Glucose, fructose, and the product of the pentose phosphate pathway may participate in nonenzymatic glycation. AGEs may further increase oxidative stress and endothelial damage. 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 extracellular matrix, reduce arterial compliance, and alter gene expression of several important intracellular molecules [104]. Both AGEs and their receptors have been localized to the target organs of diabetic complications. These receptors are found on many cells, including endothelial and smooth muscle cells. AGE-mediated nuclear factor NF- $\kappa$ B activation has been shown to increase ET-1 expression. Activation of NF- $\kappa$ B secondary to nonenzymatic glycation has also been linked to reduce NO, which would positively affect ET expression causes of diabetes complications [105].

**Vascular endothelial growth factor and angiopoietin**

Vascular endothelial growth factor (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 cardiovascular disease (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. In contrast to VEGF, the angiopoietins have little effect on endothelial proliferation. 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 (cardiovascular disease).

**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 UDP (uridine diphosphate) - N-acetyl glucosamine [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. Since G6PD activity is coupled to reduction of NADP<sup>+</sup> to NADPH, activation of the hexosamine biosynthetic pathway would further decrease NADPH / NADP<sup>+</sup> ratios. Decreased NADPH/ NADP<sup>+</sup> ratios, resulting from inhibition of G6PD or stimulation of NADPH oxidase, can increase oxidative stress by two mechanisms:

By decreasing the regeneration of the important cellular antioxidant, i.e reduced glutathione (GSH) from oxidized glutathione (GSSG).

By decreasing availability of NADPH, thereby decreasing activity of catalase, the enzyme responsible for converting the H<sub>2</sub>O<sub>2</sub>, to H<sub>2</sub>O. Indeed, glutathione 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 diabetes mellitus. 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 [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 non-pharmacological 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<sub>1c</sub>; 80-120 mg/dl (4.4-6.6 mmol/l) for the fasting plasma glucose (FPG); and 100-180 mg/dl (5.5-10 mmol/l) for a postprandial glucose [123-125].

HbA<sub>1c</sub> 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 cardiovascular diseases, 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 health care 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  $\beta$ -cell dysfunction and systemic atherosclerosis.

Recently, longer follow-up of the Diabetes control and complications trial (DCCT) and UK prospective diabetes study (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 [131].

Similarly, the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which achieved an average HbA1c of 6.4% in the treatment arm versus 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 [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.

### **Hypertension management**

Blood pressure management is a key element in the management in most patients with diabetes, particularly those who are elderly. Currently, the American Diabetes associations (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 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 cardiovascular disease.

**Lipid management**

Treatment of cholesterol disorders with HMG CoA reductase inhibitors, or “statins,” reduces the risk of first major coronary event by ~25%. The ADA recommends treatment of total cholesterol to <200 mg/dl, triglycerides to <150 mg/dl, HDL cholesterol to >40 mg/dl for men and >50 mg/dl for women, and LDL 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 level. A target LDL level of <70 mg/dl may be considered for high-risk individuals [135, 136].

**Prevention of diabetic 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. There are specific pathogenic mechanisms of 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 [137].

**Aldose reductase inhibitors**

It has been hypothesized [138] that the excessive accumulation of sorbitol is linked to certain long term complications. Thus, ALR 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 [138].

In the 1980's, 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. Others such as ponalrestat and zopolrestat were ineffective despite having more favorable side effect profiles. Zenarestat improved nerve conduction velocity and nerve morphology in a rigorous, year-long randomized, placebo-controlled trial. 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.

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. 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 mg and 20 mg doses in a 12-week, double-blinded, placebo-controlled trial.

### **Inhibitors of AGEPs**

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,  $\alpha$ -ketoglutaraldehyde 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. Antioxidants can protect against glycation-derived free radicals whereas transport proteins, for example, caeruloplasmin can bind transition metals such as cupric ions, preventing them from participating in autoxidative glycation or glycooxidation reactions.

Aminoguanidine, the first targeted AGE therapy, is a hydrazine derivative that prevents AGE formation by blocking carbonyl groups on Amadori products although it is now known to react with carbonyl groups from reducing sugars or 3-DG. 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*. 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 per day) has been shown to reduce levels of glycated haemoglobin 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 2–3 months of use [147]. AGE modulation by metformin was compared to insulin, sulfonyureas (urea derivatives), or insulin plus sulfonyureas in type 2 diabetics with similar glycemic control and no renal impairment [148].

Simvastatin treatment and adherence to an American Heart Association diet for 4 months also has been shown to decrease cellular RAGE in carotid plaques of type 2 diabetics independent of glycemic control versus dietary modifications alone. None of these studies specifically evaluated microvascular indices and further clinical trials are needed to confirm potential outcome benefits.

### **PKC 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]. While effective in treating diabetic macular edema, further studies of PCK412 were abandoned due to hepatotoxicity. Ruboxistaurin is a selective PKC- $\beta$  inhibitor that has been shown to improve retinal circulation parameters and decrease diabetic macular edema retinal leakage without significant adverse effects. Ruboxustaurin is currently pending FDA approval for the treatment of diabetic macular edema.

### **VEGF 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 [151].

**Table 1: Complications Of Diabetes**

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

**Table 2: Treatment of diabetic complications based on pathogenetic mechanisms**

Abnormality	Compound
Polyol pathway↑	Aldose reductase inhibitors Sorbitinil Tolrestat Ponalrestat Zopolrestat Zenarestat Lidorestat Fidarstate AS-3201 Epalrestat Myo-Insitol Lipoic acid, Nutriarerve
Myo-Inositol↓	Vasodilators ACE inhibitors Prostaglandin analogs
Oxidative stress↑	
Nerve hypoxia↑	PKC $\beta$ inhibitor
Protein kinase C↑	C-peptide
C-peptide↓	Nerve growth factor (NGF) BDNF
Neurotrophism↓	Acetyl-L-carnitine
LCFA metabolism↓	$\gamma$ -Linolenic acid (GLA)
GLA synthesis↓	Aminoguanidine
NEG↑	

↑- Increase; ↓- Decrease

BDNF (brain-derived neurotrophic factor); NEG (non-enzymatic glycation); LCFA (long-chain fatty acids); NBF (nerve blood flow)

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. Even though the clinical development of this compound has already been stopped.

### **Antioxidant therapy and ROS**

Vitamin E and others antioxidants act primarily to non-enzymatically 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 thiazolidinediones, angiotensin converting enzyme 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.  $\alpha$ -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].

### **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 type1 and type2 and diabetes complications. Both forms of diabetes and its complications remain amongst 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.

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