

Review Article

Advances in Clinical Endocrinology and Metabolism An Insight to Diabetes Mellitus and its Complications

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Abstract

Diabetes mellitus is a condition recognized by raised blood glucose with altered fat, metabolism, resulting from the deficiency of insulin release and function. As per the International Diabetes Federation, to date, in India 40.9 million people have diabetes and expected to raise 69.9 million by 2025. The occurrence of diabetes is increasing globally at an increased rate, earlier diabetes was found to be the low-risk disorder restricted to geriatric group, but now it becomes a major health issue, which can affect the large group of the population including all age i.e. youth and middle-aged person. Now a day's diabetic complications are the main cause of worsening diabetic patient's health. The vascular complications (both macro and micro-vascular) of diabetes mellitus, results in morbidity or death of most of the patient with the disease. The most distressing circumstances and life-threatening conditions are arising due to diabetic complications of diabetes. Thus, it is essential to recognize diabetes at the initial stage and provide suitable measure to postpone or prevent the onset of diabetes. The present review emphasizes the epidemiology, pathogenesis, and major complications and treatment of diabetes in detail.

Keywords: Diabetes mellitus, Epidemiology, Pathogenesis, Complications

Introduction

Diabetes mellitus may be defined as high blood glucose related to missing or insufficient insulin release with or without impairment of its action. According to diagnosis criteria, diabetes mellitus is categorized into four major classes: type 1 (IDDM); type 2 (NIDDM), type 3 (Gestational diabetes mellitus) and type 4 [1,2]. In other words, Diabetes Mellitus (DM) is a group of heterogeneous metabolic disorders measured by raised blood glucose level ensuing from imperfect insulin release, resistance to insulin action or both [3,4].

The WHO estimates more than 220 million people all over the world have diabetes and the number expected to be double in future by 2030 [5,6]. India, China and the United States have the largest number of diabetic patients and comprised of 35% and 45% of total diabetic patients and had Diabetic Symmetric Polyneuropathy

(DSPN). Advanced DSPN causes solemn complications like diabetic foot ulcers, gangrene and Charcot's joint, all of which get worsen the life of diabetic patients [7,8]. Diabetes mellitus characterized as hyperglycemia, is a condition that often occurs due to the imbalance in insulin level, i.e deficiency in insulin synthesis and release and its function or both. The enormous cases of diabetes divided into two pathogenetic categories. In type 1 diabetes, the basis is total absence of insulin secretion while in type-2 occurs due to insufficient secretion and improper insulin action [9,10]. In spite of the latest developments of the new drugs for prevention of complications, still attention in the technical area needs to reach the inaccessible natural products to be tested in humans [11,12]. So clinical and preclinical trials may be one attempt to control diabetes and attenuate its complications during pregnancy in both experimental animals as well as in women and [13,14]. *Azadirachta Indica* commonly known as neem tree in India and Burma renowned for

its medicinal properties. It is used as an antibiotic and for treatment of Chagas disease but the antidiabetic actions have only been confirmed in non-pregnant animals [2]. The worldwide occurrence of diabetes is estimated to be increased up to 8.5% by 2025. WHO predicts that the prevalence of DM is more common in developing countries. In the last decade, studies performed in India have highlighted that not only the occurrence of diabetes is high but also it is rising quickly and is expected to rise up to 57.2 million [15]. Drugs used regularly to take care of diabetes are sulfonylurea, biguanides, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, insulin, etc. [16]. According to WHO the Diabetes diagnostic include Fasting glucose [4,9], glucose level in 2 hours of food and Glycated Haemoglobin (HbA_{1c}) as mentioned in table 1.

Epidemiology of diabetes

As the prevalence of diabetes today it shows 8.8% among adults, nearly double the rate of 4.7% then in 1980 and it is expected to rise up to 9.9 per cent till 2045 [14]. Type 2 diabetes incidence indicates higher rates in males in comparison to females, may be due to sex-related difference in sensitivity, obesity and excess accumulation of fat, and other causative factors like raised blood pressure or habits like consuming alcohol or smoking may be increased the risk of diabetes in males [17].

Till 2016 more than 422 million populations are diabetic, which is quite high if compared with 108 million, 382 million in 1980 and 2013 respectively. Out of which 90% of the cases are of Type 2. Though the occurrence of diabetes is equal in both women and men, but reports showed male are at higher risk of diabetes due to physiological alteration and some habits of consumption of cigarette or alcohol which may lead to generation of free radicals [3,6] and may be reduced by taking sufficient amount of antioxidants. The detail etiology is mentioned in figure 1. That shows the factors could increase the risk for diabetes which includes infection, Major Disorders, Genetics, Habits and sedentary life styles [17,18].

Types of diabetes

Diabetes are of two focal types i.e., type 1 and type 2 with their relative significance and another category is gestational diabetes mellitus detail mentioned in table 2.

Type 1 diabetes

IDDM is commonly known as Type I Diabetes: In this disease, the β -cells of the pancreas are partially or completely degenerate, so not able to synthesize sufficient

amount of insulin, a hormone which helps in the utilization of blood sugar (glucose) for production of energy [19]. Hypoglycemia is the condition where adequate glucose will not reach to the cell and patients show irritability and in severe deficiency of glucose to the brain, tissues may lead to oblivion or death. Hyperglycemia and long-lasting insulin deficiency may develop ketoacidosis, which shows increase ketone bodies in blood, due to the utilization of fat for production of energy. The accumulation of Ketone bodies leads to alter blood pH to acidic, which decelerate the other metabolic functions. This may lead to coma or death [19,20].

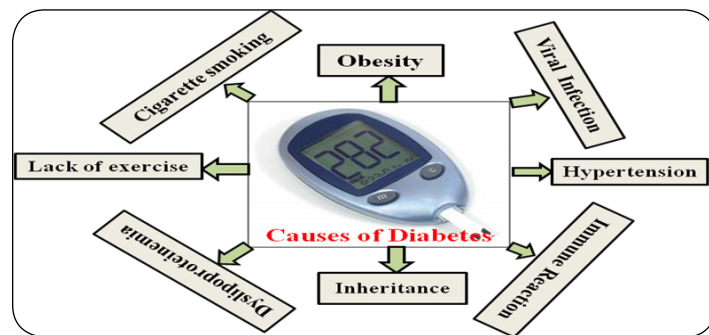


Figure 1: Etiology of diabetes.

Type 2 diabetes

NIDDM commonly recognized as Type 2 diabetes is a compound metabolic disorder. The heritable and ecological factors commonly result in homogeneous and progressive alteration in pancreatic β -cell dysfunction that results in insulin resistance. Obesity and hyperlipidemia are chief contributors to the insulin resistance and impair glucose tolerance. Irregularity in the secretion of additional hormones such as increased level of incretin, Glucagon-Like Peptide 1 (GLP-1) and raised concentrations of other counter-regulatory hormones in circulation leads to insulin resistance [21]. Insulin resistance occurs via several pathways out of which one includes the concentrations of hormones (eg: augmented leptin, compact adiponectin, and increased glucagon, increased cytokines level) where as others like (tumour necrosis factor, interleukin alpha), and suppressors of cytokine signal and other challenging signals are retinol-binding protein [22]. Concurrent alterations in β -cell function frequently comprise a period of compensatory hyperinsulinemia with irregular secretion. When insulin discharge is not enough to conquer insulin resistance, glucose intolerance progresses to type 2 diabetes. The decreased number of β -cell leads to persistent hyperglycemia improper fat metabolism, generation of oxidative stress, inflammation. NIDDM Patients typically have α -cell dysfunction that results due to increased glucagon release in hyperglycemic condition

absolutely due to prandial GLP-1 secretion [13,22,23].

Gestational diabetes

Gestational Diabetes Mellitus (GDM) may be defined as any irregular carbohydrate fanaticism that begins or seen first time in pregnancy. It does not eliminate the risk that unknown glucose prejudice and has proceeded during pregnancy. GDM complicates about 7% of pregnancy, which accounts for 2, 00,000 cases per annum. Recent study revealed i.e 18.9% of incidence of GDM are from India is [24].

Pathogenesis of diabetes

Type 1 diabetes: Type 1 diabetes mellitus is a chronic autoimmune disease connected with discriminating the insulin-producing β -cells of pancreatic. The beginning of clinical disease represents the end step of β -cell demolition important to type 1 diabetes mellitus. Some features describe type 1 diabetes mellitus as an autoimmune disease [25,26]. Organization of weakness to disease with the class II (immune response) genes of the Main Histocompatibility Compound (MHC), Human Leucocyte Antigens (HLA). Presences of islet cell-specific auto-antibodies are the main cause behind the disease. The involvement of monokines and TH1 cells producing interleukins has also their role in disease progression.

The pathogenesis of discriminating β -cell damage inside the islet in type 1 DM is complicated to go after due to the patent heterogeneity of the pancreatic lesions. At the onset of evident hyperglycemia, a mixture of pseudoatrophic islets cells producing glycogen somatostatin (d cells) and Pancreatic Polypeptide (PP cells) and islets containing both b-cells causes infiltrating lymphocytes and monocytes may be seen [25]. Lymphocytic infiltration occur in the islet containing left behind β -cells and found in type 1 DM, which reflects this heterogeneity of islet lesions. Activation of islet antigen-specific CD4+ T cells appears to be the absolute prerequisite for the development of diabetes in all animal models of type 1 DM [26]. CD4+ islet-specific T-cell clones were isolated from diabetic NOD mice, when injected into prediabetic or non-diabetes-prone Fl mice, induce insulinitis and diabetes. The report indicates that higher concentration of CD4+ T cells is sufficient to induce insulinitis while CD8+ T cells donate to the severity of the damage. These findings jointly confirmed that insulinitis in chronic graft against host disease may occur in the nonappearance of CD8+ T cells suggest that CD4+ T cells may be the only immunocompetent cells requisite in the disease process. Whereas CD4+ T cell having alloantigen

RT6 are missing in diabetes-prone BB rats and appear to defend rats from MLD-STZ induced diabetes. Down-regulation of diabetogenic autoimmune response by the spleen cells derived from animals treated with adjuvants, explained the role of CD4+ T cell subsets [27]. High level of TH₁ type cytokines and IL-2 and interferons are found to correlate or to enhance induction of autoimmune diabetes in experimental models [28,29]. In animal, models of type 1 DM studies indicate pancreatic macrophages are the first cell type invading the islets [30]. In vitro and ex-vivo studies of perfused pancreas shows that Interleukin 1 (IL-1) and Tumor Necrosis Factor (TNF), are two major cytokines produced by macrophages, induce structural changes of β -cells and suppression of their insulin releasing capacity [31]. However, it seems that IL-1 and TNF do not contribute appreciably to the cytotoxic activity of macrophages [32]. Interferon alfa is also a powerful activator of macrophages for nitric oxide synthesis. Recently, evidence has been provided indicating that no synthase activity is involved in diabetes development [4,33]. The evidence based report indicated that nitric oxide may be an important factor in regulating immunity and recommended an option that a new class of immunopharmacological agents, responsible for modulating nitric oxide secretion may be screened to avoid type 1 DM prevalence [34,35]. Table 3 mentioned various causes behind the insulin resistance.

Type 2 diabetes: Below normal physiological conditions, plasma glucose concentrations are maintained within a slight range, in spite of wide fluctuations in contribute and demand, during a tightly regulated and dynamic communication between tissue sensitivity to insulin (especially in liver) and insulin secretion [36]. In type 2 diabetes these mechanisms break down, with the result that the two major pathological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β -cell, and impaired insulin action through insulin resistance [37]. Type 2 diabetes mellitus has a superior genetic organization than type 1 DM, the pathogenesis of type 2 diabetes mellitus is categorized by impaired insulin secretion and insulin resistance as shown in figure 2. The 100% concordance rate in equal twins is thought to be over-estimated, due to a choice or treatment bias. A population based twin study in Finland has shown a concordance rate of 40%, and ecological effect may be a likely cause for the superior concordance rate for type 2 diabetes mellitus than for type 1 diabetes mellitus [38]. Type 2 diabetes mellitus affects 1 to 2% of caucasians but it is much superior in some ethnic groups such as Pima Indians [39] and Arabs [40] and approach 50% in

South India. This indicates that genetic factors are more significant than ecological factors. Except for Maturity Beginning Diabetes of the Young (MODY), the mode of inheritance for type 2 diabetes mellitus is unclear. MODY, inherited as an autosomal dominant trait, may result from mutations in glucokinase gene on chromosome 7p. Glucokinase is a key enzyme of glucose metabolism in beta cells and the liver [7,41]. Maturity onset diabetes of the young (MODY) is defined as hyperglycemia diagnose before the age of 25 years and which is treatable for more than 5 years without insulin in cases where Islet Cell Antibodies (ICA) are unresponsive and HLA-DR3 and DR4 are heterozygous. MODY is uncommon in Caucasians, less than 1%, and extra regular in blacks and Indians, more than 10% of diabetics. Chronic difficulties in MODY were thought to be uncommon but later were originate to be further common, representative its heterogeneity [42].

Allowing for MODY as a divide unit may masquerade its organization with specific genetic diseases; and without a definite genetic marker, it should be treated as type 1 DM [43]. Identification of a gibberish mutation in the glucokinase gene and its linkage with MODY was identified first time by a French family, implicating mutation in a particular gene responsible for glucose metabolism in the pathogenesis of type 2 diabetes mellitus [44,45].

Gestational diabetes: Insulin resistance and damage beta cell function, regularly add to GDM. Pregnancy is a diabetogenic condition considered by impaired insulin compassion. This is largely recognized as the pregnancy enters the 2nd trimester. The main contributor are the placental hormones particularly, human placental lactogen, progesterone, cortisol, growth hormone and prolactin. These hormones cause decrease phosphorylation of insulin receptor substrate and so reflective insulin resistance. Cytokines similar to tissue necrosis cause have also been unavailable in pathogenesis of insulin resistance. Logically, the pancreas should compensate for this exact by increasing insulin secretion. However, in GDM there is decline of β cell function, mainly the first phase insulin secretion. In a study on Latino women with GDM, 67% reduction of β cell function was well-known as compared to the regular pregnant organize. The second phase insulin release is similar to that in person with normal glucose tolerance. The defects in β cell have been credited either to autoimmune improvement or enzymatic defect like glucokinase. Autoimmunity should be supposed in women who do not have typical characteristics of

increased risk of GDM, i.e., who are lean and Caucasians. Thus, the combination of insulin resistance and secretary defect during pregnancy results in GDM [46]. Table 4 summarizes different conditions and treatment measures of Type 1 and Type II diabetes.

Complications of diabetes

The microvascular and macrovascular complications of DM lead to the morbidity and mortality. Whereas poor control of blood sugar and prolonged illness seem to be the most important risk factors for these complications, evidence suggests that ethnic variability in might also exist for diabetes [47], the type of complications are mentioned in figure 2.

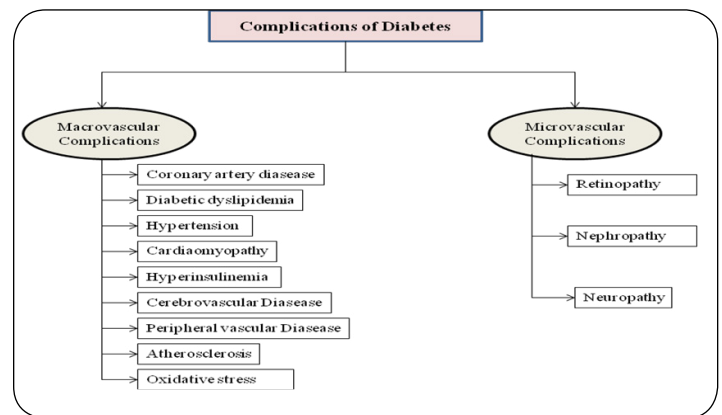


Figure 2: Complications of diabetes and associated disorders.

Microvascular complications

Diabetic retinopathy: Diabetic retinopathy is the most common microvascular complication in diabetes. The initial diabetic retinopathy or other microvascular complications of diabetes depends on the period as well as the progress of hyperglycemia. Patients with type 2 diabetes were originating to be associated to the equal severity of hyperglycemia and develop hypertension in Patients, whereas type 1 diabetes mainly shows retinopathy. Retinopathy may start to develop as early as 7 years before the diagnosis in patients with type 2 diabetes [20,47].

Mechanism: Aldose reductase may be the important contributor for the onset of diabetes complications. Aldose reductase is essential for the intracellular polyol pathway. This pathway involves the exchange of glucose into sorbitol. High glucose levels increase the change of sugar molecules during the polyol pathway, which leads to raised sorbitol in cells. Stress dreads to develop osmotic stress and acts as an original mechanism behind

the increased microvascular complications in diabetes. However treatment with aldose reductase inhibitors were not shown any positive results [48].

Diabetic nephropathy: Diabetic nephropathy is the leading cause of renal failure Diabetic Patient. Normal Individual shows proteinuria > 500 mg in 24 hours, while in diabetes urea contains low Albumin or commonly known as Microalbuminuria. These sequences are similar for both type 1 and type 2 diabetes. As several as 7% of patients with type 2 diabetes may previously have microalbuminuria. In diabetes the functional change of the kidney shows increased thickness of glomerular basement membrane with microaneurysm formation [46].

Mechanism: Micro albuminuria is the main symptom found in patients with type 1 and type 2 diabetes. Treatment with Angiotensin-Converting Enzyme (ACE) inhibitors has not been shown to stop the development of microalbuminuria in patients with type 1 diabetes but has been shown to decrease the danger of initial nephropathy and cardiovascular actions in patients with type 2 diabetes. Renin-angiotensin system inhibitors has good role over the other antihypertensives in patients with diabetic nephropathy. Both ACE inhibitors and ARBs have been shown to reduce the danger of sequence to macroalbuminuria in patients with microalbuminuria up to 60-70%. These drugs are suggested as the first-line pharmacological treatment of microalbuminuria, even if patients are normotensive [49].

Patients suffering from macro albuminuria, conditions will be improved by controlling hypertension. Hypertension of these patients with microalbuminuria has slower Glomerular Filtration Rate (GFR). Whereas combination therapy of ARB with others has been exposed to have added renoprotective effects. It should be well-known that patients treated with these drugs (particularly in grouping) may understand an original increase in creatinine and have to be monitored for hyperkalemia. The considerable increase in creatinine after begin of these agents should punctual an estimate for renal artery stenosis [47].

Peripheral neuropathy: Peripheral neuropathy is various types include sensory, focal/multifocal, and autonomic neuropathies. Chronic sensorimotor distal symmetric polyneuropathy is a category of neuropathy in diabetes. Normally, patients complain burning, irritating, and stimulatory pain, but occasionally they

observe simple numbness. In patients who have pain, it may be inferior at night. Patients with simple numbness are capable of the present with a painless bottom ulceration, consequently it is major to distinguish that require of symptoms does not rule out the occurrence of neuropathy. Physical estimation reveals sensory defeat to light touch, vibration, and heat. Patients also usually experience defeat of ankle impulse. Symptoms are usually most important at night mononeuropathies normally have extra sudden onset and engage almost any nerve, but most generally the median, ulnar, and radial nerves are affected. Cranial neuropathies are there but rare. There is no precise action of diabetic neuropathy. The various study comprises optional that organize of hyperglycemia and avoidance of glycemic expedition may improve symptoms of peripheral neuropathy. Amitriptyline, imipramine, paroxetine, citalopram, gabapentin, pregabalin, carbamazepine, topiramate, duloxetine, tramadol, and oxycodone and are useful to treat painful symptoms, but simply duloxetine and pregabalin are commonly used for painful peripheral diabetic neuropathy. Treatment of autonomic neuropathy is focused toward the organs that is affected but also includes regulation of glycemic control [35,48].

Mechanism: The type of injury occurs to the peripheral nerves due to hyperglycemia is not recognized other than the possible causes like polyol addition, injury due to AGEs, and presence of oxidative stress [5,15].

Macrovascular Complications

More than 65% of patients with T2DM died every year due to cardiovascular disease out of which 80% due to Coronary Artery Disease (CAD) [12,50] Compared with white individuals, CAD tends to develop a decade or two earlier and triple vessel diseases is more common; mortality after an acute coronary event is also 40% higher in Asian Indian patients [51]. The presence of T2DM seems to confer a 3-4 times higher risk of cardiovascular disease to Asian Indian individuals than to their white counterparts, even after adjusting for sex, age, smoking status, hypertension and obesity [52].

Mechanism: Possible explanations include the atherogenic milieu promoted by high levels of insulin resistance and the high prevalence of 'atherogenic dyslipidaemia' characterized by high levels of triglycerides and small dense LDL cholesterol, and low levels of HDL cholesterol. The important pathology involved in macrovascular condition is the atherosclerosis, which impedes the blood flow into the arterial walls.

Atherosclerosis is appearance to result from chronic inflammation and injury to the arterial wall in the marginal or coronary vascular association. In reply to endothelial injury and inflammation, oxidized lipids from LDL particle gather up in the endothelial wall of arteries. Angiotensin II may well continue the oxidation of such particles [51].

Prevention of diabetes

Higher levels of physical action diminishes the risk of diabetes upto 28%, whereas diet control known to be successful in avoiding diabetes and comprises of a diet rich in whole grains and fiber, and using good fats, such as the polyunsaturated fats in nuts, vegetable oils, and fish. Tobacco smoking is also associated with an increased risk of diabetes and its complications, so smoking cessation can be an important preventive measure as well [1].

The connection between type 2 diabetes and the main regulating risk factors (excess weight, damaging diet, physical immobility and tobacco use) is comparable in all region of the world. There is evidence that the underlying intrinsic factors of diabetes are the reflection of the other driving forces like socio-economical and cultural diversity, globalization, urbanization, geriatric group, and finally the environment [21,53].

Management of diabetes

Diabetes mellitus is a chronic disease, in which there is no definite cure except in very precise situation. Management depend on maintenance of blood glucose levels as equivalent to normal, without causing low blood sugar. This can be controlled with a healthy diet, weight loss, regular exercise and use of appropriate drugs (insulin in the case of type 1 diabetes; oral medications, as well as probably insulin, in type 2 diabetes) [54]. Education is an important tool for prevalence of the disease and helpful in the treatment, though complications are rare in normal and less common in people who have well-maintained blood sugar levels. Whereas the risk factors comprises of smoking, raised cholesterol, obesity, elevated blood pressure, and lack of exercise. Specialized shoes are available to reduce the risk of foot-ulceration, or re-ulceration, in high risk patients [55].

Non Pharmacological Approaches: Lifestyle Modification

Patients with diabetes can be educated regarding the disease and treatment, good nutrition to accomplish a normal body weight, and implement, with the objective

of maintenance both short-term and long-term blood glucose levels within acceptable bounds. In adding, given the connected higher risks of cardiovascular disease, existence modifications are suggested to manage blood pressure. There is no single dietary guide that is unsurpassed for all people with diabetes. For overweight populace with type 2 diabetes, any diet that the individual will attach on to and accomplish weight loss on is successful [56,57].

Pharmacological Approaches: With Medications

Medication used to treat diabetes includes controlling blood sugar levels. There are dissimilar course of anti-diabetic medication. Few taken orally like metformin, while others are simply accessible by parenteral route such as GLP-1 agonists. Type 1 can be treated with insulin, or with a combination of standard and NPH insulin, or synthetic insulin analogs. Oral hypoglycemic drugs are worked by decreasing the liver production of glucose [58]. These agents help in increase insulin release, and also decrease the absorption of sugar from the bowels, and agents that create the body extra sensitive to insulin. Insulin is given in type 2 DM, while a long-acting formulation will not work for regulating blood glucose level [14,59].

Aspirin is also recommended to improve outcomes in uncomplicated diabetes with hypertension [57]. Herbal remedies are another major approach for control of blood glucose level [12,19].

Weight loss in type-2 diabetes is a successful measure.

The BMI is reduced after surgery but the mechanism is unclear, it is suggested that this option is true in those patients who are unable to manage their body weight and glucose level in hand [9,16,60]. Pancreas transplant is an alternative measure for those with type 1 diabetes who have severe complications, like end-stage kidney disease, which require kidney transplantation [61-64].

Recent advancement

Insulin Inhalor Afrezza of Mankind was approved by the FDA but unfortunately withdrawn from market due to their unwanted effects. The significance was these are convenient and easy to take. Transdermal insulin was developed and applied as cream and under post marketing surveillance in type 2 diabetic patients [4].

Conclusions

Diabetes mellitus is the commonest type of metabolic disorder associated with multiple complications. In diabetes, alteration occurs to carbohydrate, fat, and protein metabolism, which results in the partial or total destruction of beta cells of the pancreas, which shows absolute or partial insulin deficiency or insulin resistance. Other associated long-term complications of diabetes are macrovascular and microvascular. For example, either major or minor organs/ system are involved examples such as Nephrolithiasis, brain stroke, blindness, cardiac disorders like hypertension and diabetic neuropathy. The pathophysiological mechanism of diabetic complications is multidirectional and complex. In the present review, the mechanisms of the pathogenesis implicated in diabetic complications are covered including both microvascular and macrovascular changes including immunological systems. The current conventional therapy used to reduce hyperglycemia during diabetes is not sufficient. Therefore, an increased understanding of diabetic complications and their pathogenesis may raise a new path for the discovery of new chemical/ herbal moiety to treat diabetes as well as its complications.

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Conflict of interest

All authors have approved the final manuscript and no potential conflict of interest was reported by the authors.

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