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# Diabetes mellitus: A comprehensive review

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**Abstract**
Diabetes mellitus (DM) is a group of metabolic diseases in which a person has high blood sugar. In this disease either the body does not produce enough insulin, or cells do not respond to the insulin that is produced. High blood glucose levels are manifested during diabetes mellitus because of inadequate pancreatic insulin secretion or poor insulin-directed mobilization of cellular glucose. Etiologically, diabetes has been divided into three types namely: Type 1 DM or insulin-dependent diabetes mellitus (IDDM) in which body fails to produce insulin, and presently requires the person to inject insulin. Type 2 DM or non-insulin-dependent diabetes mellitus (NIDDM), results from insulin resistance, a condition where cells fail to use insulin properly, with or without an absolute insulin deficiency. The third main type is gestational diabetes which occurs when women without a previous history of diabetes develop a high blood glucose level during her pregnancy. Currently available pharmacotherapy for the treatment of diabetes mellitus includes insulin and oral hypoglycemic agents. Such drugs acts by either increasing the secretion of insulin from pancreas or reducing plasma glucose concentrations by increasing glucose uptake and decreasing gluconeogenesis. But the currently available drugs do not restore normal glucose homeostasis effectively for a long time. Moreover they are not free from side effects like hypoglycemia, kidney diseases, GIT problems, hepatotoxicity, heart risk problems, insulinoma. Besides these are to be continued rest of life. Various herbal remedies are proved to be effective in the treatment of diabetes. The present review therefore is an attempt to focus on the physiological aspects of diabetes, its complications, goals of management, and treatment of diabetes.

**Keywords:** Insulin, blood glucose levels, Insulinoma, hyperinsulinemia, hyperglycemia

## Introduction
Diabetes mellitus is a cluster of heterogeneous disorders showing episodes of hyperglycemia and glucose intolerance. It develops due to lack of insulin, impaired insulin action, or both (Sicree *et al.*, 2006) [1]. These complications arise as a result of derangements in the regulatory systems for storage and mobilization of metabolic fuels, which includes the catabolism and anabolism of carbohydrates, lipids and proteins due to defective insulin secretion, insulin action, or both (Shillitoe, 1988; Votey and Peters, 2004) [2, 3]. Classification of diabetes mellitus is based on its diagnostics and clinical manifestations. Based on this, there are four types or classes of diabetes mellitus like, type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types (Sicree *et al.*, 2006) [1]. Type 1 diabetes accounts for only a minority of the total burden of diabetes in a population but its incidence is increasing in both rich and poor countries. Moreover, a shift towards type 1 diabetes is occurring in children at earlier ages (Sicree *et al.*, 2006) [1]. 85 to 95% of all diabetes in rich and developing countries are of type 2. It has an association with improper utilization of insulin by target cells and tissues. It is currently a common and serious health concern worldwide. According to WHO (1994), this problem has been aggravated by rapid cultural and social dynamics, ageing populations, increasing urbanization, dietary changes, reduced physical activity and other unhealthy lifestyle and behavioral patterns. Diabetes mellitus and impaired glucose tolerance, can now be found in almost every population in the world and this trend is on the rise globally (WHO, 1994) [4].

## Etymology of diabetes mellitus
The terms "Diabetes" and “Mellitus” have come from Greek where “Diabetes” denotes "a passer through a siphon" and "Mellitus" refers to "sweet". The Greeks named it as the excessive amounts of urine produced by diabetes patients attracted flies and bees. The ancient Chinese diagnosed diabetes mellitus by observing whether ants are attracted to a person's urine or not. In medieval ages, the European doctors tested for diabetes by testing the urine themselves (Patlak, 2002) [5].

**History of diabetes mellitus**

Though treatments of diabetes were known since the Middle Ages, its pathogenesis elucidation occurred mainly in the 20th century. The role of the pancreas in diabetes was discovered by Joseph Von Mering and Oskar Minkowski in 1889. In 1910, Sir Edward Albert Sharpey-Schafer suggested that diabetics individuals lacked a single chemical which was normally produced by the pancreas and later this chemical was named as insulin (Himsworth, 1936) [6]. In 1921, Frederick Grant Banting and Charles Herbert Best isolated insulin from bovine pancreases at the University of Toronto in Canada. Later Sir Harold Percival made the distinction between type I and type II diabetes (Himsworth, 1936) [6]. Other historical discoveries in this field are: identification of sulfonylureas in 1942, the radioimmunoassay for insulin discovered by Rosalyn Yallow and Solomon Berson, discovery of the metabolic syndrome by Reaven in 1988 and identification of thiazolidinediones in the 1990s in the treatment of diabetes (Patlak, 2002) [5].

**Prevalence of diabetes mellitus**

Diabetes is one of the largest global health burdens of this century. Each year more and more people becoming prone to this life-changing complication. About 415 million adults are estimated to currently have diabetes but many countries are still unaware of the social and economic impact of this disease. This lack of understanding is the biggest barrier to effective prevention strategies of diabetes (IDF, 2015) [7]

Most regions over the globe are facing a continuous increase in diabetics. The Western Pacific Region has 153 million adults with diabetes whereas the North America and Caribbean Region has one out of eight adults with the disease. Europe has approximately 140,000 number of children with type 1 diabetes. In the South-East Asia Region, 24.2% of all live births face high blood glucose during pregnancy. In the Middle East and North Africa Region, two out of five adults with diabetes remain undiagnosed. By 2040, in the South and Central America Region, the number of people with diabetes will increase by 65%. In the Africa Region between 9.5 million and 29.3 million people live with diabetes according to the report of 2015.

**Economic burden of diabetes mellitus**

Diabetes mellitus is a very expensive disease in terms of its long-term microvascular and macrovascular complications and their treatment cost. These complications hampers both life expectancy and quality of life (Ashcroft and Ashcroft, 1992; Collins, 2002; Votey and Peters, 2004) [8, 9, 3]. According to Kirigia *et al.* (2009) [10], diabetes mellitus poses a big economic burden with regards to health system costs, indirect costs arising from patient disability and premature mortality, time spent by family members, and intangible costs of psychological pain to the family and loved ones. Barcelo *et al.* (2003) [11] estimated total annual cost of diabetes in Latin America and the Caribbean to be US$65.216 billion. With type 1 diabetics in India, Shobhana *et al.* (2002) [12] estimated that the cost of treatment could be as high as US$50 million. According to American Diabetes Association, the combined direct and indirect costs of diabetes in 1997 were estimated at US$98 billion in the United States of America. Total direct costs of diabetes in Spain is over US$650 million in 1994 according to Hart *et al.*, (1997) [13]. In England and Wales, the estimated cost of type 1 diabetes is US$1.92 million according to Gray and Fenn (1995) [14]. As Kirigia *et al.* (2009) [10] indicate, the effectiveness of prevention and control of those illnesses rely largely on the performance of health systems, functions of leadership and governance; health workforce; medical products, vaccines and technologies; information; financing; and services delivery.

**Classification of diabetes mellitus**

**Table 1:** Classification of diabetes mellitus (Deepthi *et al.*, 2017) [15]

| Type | Characteristics feature |
|---|---|
| Type 1 (1a and 1b) | Secretion of insulin was reduced due to damage of β-cells Own body tissues are damaged by self-antibodies. |
| Type 2 | Insulin scantiness occur due to Insulin secretion and insulin resistance. Imperfection of ß-cell functions genetically. Failure in insulin secretion genetically. |
| Other specific types | Pancreatic endocrinopathy. Indigenous infections like rubella and cytomegalovirus induced by drugs or chemicals. Other genetic indisposition. |
| Gestational diabetes | Temporary and appears during third trimester of pregnancy. After delivery, blood sugar levels generally return to normal. |

**Type 1 diabetes**

Auto immune response: It is expressed as a consequence of autoimmune disease (Reuveni *et al.* 2016; Zou *et al.*, 2016; Yanqiang *et al.*, 2016; Allen *et al.*, 2015; Zhang, 2013) [16, 17, 18, 19] where the beta cells of pancreas are slowly demolished by the body's own immune system which reduces insulin production.

Genetic factors: Investigators have designated at least 18 genetic positions as IDDM1-IDDM18 (Insulin dependent diabetes mellitus), which are related to type 1 diabetes. The IDDM1 (Insulin dependent diabetes mellitus) region contains the HLA (Human leukocyte antigen) genes that encode proteins called major histocompatibility complex. In this location immune responses are affected by these genes.

Environmental factors: Due to abrupt stress like an infection where the β-cells of pancreas falls below 5-10%. Coxsackie viruses are a family of enteric viruses which attack the intestinal tract leading to the destruction of insulin producing pancreatic β cells.

**Type 2 diabetes**

Type 2 Diabetes ranges from Insulin Resistance with Relative Insulin Deficiency to Predominantly an Insulin Secretory Defect with Insulin Resistance. This form of diabetes accounts for 90-95% of diabetes. It was previously referred to as non-insulin dependent diabetes, type 2 diabetes, or adult-onset diabetes. It encompasses individuals with insulin resistance and relative (rather than absolute) insulin deficiency. The specific etiologies are still unknown. Autoimmune destruction of b-cells does not occur in this case. Most patients are found obese and this obesity itself causes some degree of insulin resistance. Ketoacidosis often occurs spontaneously in this diabetes. Type 2 diabetes frequently remains undiagnosed because of gradual onset of

hyperglycemia and at earlier stages the patient shows none of the classic symptoms of diabetes. Risk for development of macrovascular and microvascular complications is greater here. Whereas patients with this diabetes may have normal or elevated insulin levels. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Weight reduction and/or pharmacological treatment of hyperglycemia may improve insulin resistance. The risk of onset of this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior Gestational Diabetes Mellitus and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ ethnic subgroups. A strong genetic predisposition is often observed here. However, the complex genetics of this form of diabetes are not fully defined.

This kind of diabetes also has a powerful genetic predisposition. It is suggesting that twins have 100% approaching rate for diabetes. Nearly 85% of population with type 2 diabetes (Tiki 2016; Yamada *et al.,* 2016; Nealon *et al.,* 2016) [20, 21, 22] are obese that causes insulin resistance. To predict the risk of type 2 Body Mass Index (BMI) is used as a measure.

**Drug-or chemical-induced diabetes**

Many drugs impairing insulin secretion may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance. Certain toxins such as Vacor (a rat poison) and intravenous pentamidine can permanently destroy pancreatic b-cells. Many drugs and hormones like nicotinic acid and glucocorticoids can impair insulin action.

**Infections related diabetes**

Diabetes occurs in patients infected with congenital rubella, coxsackievirus B, cytomegalovirus, adenovirus, and mumps.

**Uncommon forms of diabetes**

In this category, there are two known conditions, and others are likely to occur. The stiff-man syndrome is an autoimmune disorder where patients usually have high titers of the GAD autoantibodies, and one-third of them develop diabetes. Anti-insulin receptor antibodies can cause diabetes. They bind to the insulin receptor and block the binding of insulin to its receptor of target tissues. Anti-insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases. In case of extreme insulin resistance, patients with anti-insulin receptor antibodies exhibit acanthosis nigricans and this syndrome was termed type B insulin resistance.

**Other genetic syndromes sometimes associated with diabetes**

Many genetic syndromes like the chromosomal abnormalities of Down syndrome, Klinefelter syndrome, and Turner syndrome are accompanied by an increased incidence of diabetes. Wolfram syndrome is an autosomal recessive disorder presenting insulin-deficient diabetes and the absence of b-cells at autopsy. Other manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness.

**Genetic involvement of diabetes**

The most common mutation occurs at position 3,243 in the tRNA leucine gene, leading to an A-to-G transition and this point mutation is associated with Diabetes. Genetic abnormalities causing the inability to convert proinsulin to insulin have been identified is inherited in an autosomal dominant pattern. The resultant glucose intolerance is mild. Similarly, the production of mutant insulin molecules with resultant impaired receptor binding is associated with an autosomal inheritance and only mildly impaired or even normal glucose metabolism.

Genes proposed to be associated with type 2 diabetes risk include:

- TCF7L2, affecting insulin secretion and glucose production
- the sulfonylurea urea receptor (ABCC8), which plays role in regulation of insulin
- Calpain 10, associated with type 2 diabetes risk in Mexican Americans
- glucose transporter 2 (GLUT2), which helps glucose to move into the pancreas
- The glucagon receptor (GCGR), a glucagon hormone engaged in glucose regulation (Winter, 2014) [23].

**Biochemical background of diabetes mellitus**

Glucose is the body's primary energy source circulating in the blood as a mobilizable fuel source for living cells (Piero, 2006; Kibiti, 2006; Njagi, 2006) [24, 25, 26]. A pancreatic hormone, insulin is responsible for blood glucose level regulation. Its receptor sites locate on peripheral side of the cell membranes. It affords entry of glucose into respiring cells and tissues via requisite channels. Insulin stimulates catabolism on glucose into pyruvate through glycolysis. It also upregulates glycogenesis from excessive cytosolic glucose and lipogenesis from excessive cytosolic acetyl-CoA. These metabolic events are antagonistic to metabolic events triggered by the hormone glucagon. At or below threshold level, glucose stays in the blood instead of entering the cells (Belinda, 2004) [27] when the body attempts to arrest hyperglycemia, by drawing water out of the cells and into the bloodstream. The excess sugar is excreted in the urine. As a result, diabetics present with constant thirst, drinking large amounts of water. So, polyuria develops as the cells try to get rid of the extra glucose. This subsequently leads to glucosuria (Piero, 2006) [24]. As hyperglycemia prolongs, the body cells are devoid of glucose due to the lack of insulin. Then the cells start to seek alternative mobilizable energy sources. In this regard, the cells turn to fatty acids stored in adipose tissue. The fats are not fuel sources for the red blood cells, kidney cortex and the brain. The red blood cells lack mitochondria in which beta-oxidation pathway rests. The fatty acids cannot pass the blood-brain barrier. To supply energy to such cells and tissues, the acetyl-CoA arising from catabolism of fatty acids is diverted to ketogenesis to produce ketone bodies. This in turn serve as alternative fuel sources for such cells and tissues. These ketone bodies are also passed in the urine, thereby leading to ketonuria, which characterizes diabetes mellitus. Buildup of ketone bodies in the blood produces ketosis. Ketone bodies are acidic in nature which lower blood pH, leading to acidosis. This resultant combination of ketosis and acidosis leads to a condition called ketoacidosis. If left untreated, ketoacidosis leads to coma and death (Belinda, 2004) [27].

**Pathophysiological aspects**

Type 2 DM is characterized by insulin insensitivity due to insulin resistance which declines insulin production, and eventual pancreatic beta-cell failure. This leads to a decrease in glucose transport into the liver, muscle cells and fat cells.

There is an increase in the breakdown of fat with hyperglycemia (Kahn 1994) [28]. Type 1 diabetic patients are usually young (children or adolescents) and not obese when they first develop symptoms. There is an inherited predisposition, with a 10-fold increased incidence in first-degree relatives of an index case, and strong associations with particular histocompatibility antigens (HLA types). Experiment with identical twins have shown that genetically predisposed individuals require to be exposed to an environmental factor like viral infection. Viral infection may damage pancreatic B cells and expose antigens that initiate a self-perpetuating autoimmune process. The patient becomes overtly diabetic only when more than 90% of the beta cells have been destroyed. In this type, insulin deficiency attenuates long term potentiating and might lead to deficits in learning and memory. Type 2 diabetes is accompanied both by insulin resistance and by impaired insulin secretion, each of which are important in its pathogenesis. Such patients are often obese and usually present in adult life, the incidence rising progressively with age as B-cell function declines. Later this insulin resistance leads to both Aβ plaque formation as well as tau hyperphosphorylation. During hyperinsulinemia, insulin and Aβ competes for insulin degrading enzyme, leading to Aβ accumulation and plaque formation. A decrease in insulin receptor signaling leads to inhibition of Akt and dephosphorylation (activation) of GSK-3β and results in tau hyperphosphorylation (Rang and Dale, 2007; Robertson, 1995) [29, 30]

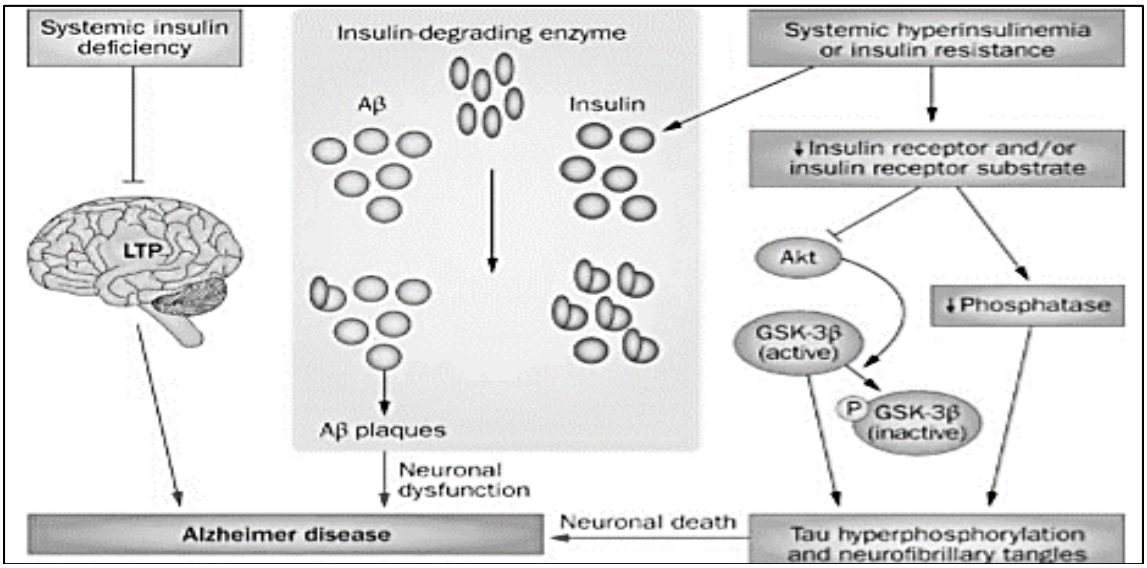


**Fig 1:** Pathophysiology of Type I and Type II diabetes. Abbreviations: Aβ- Amyloid- β, GSK-3β-glycogen synthase kinase 3β, LTP- long term potentiation, P- Phosphate (Chinmay *et al.*, 2015) [31]

As the disease progresses, tissue or vascular damage ensues severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Long standing type 1 DM patients are susceptible to microvascular complications; and macrovascular disease (coronary artery, heart and peripheral vascular diseases) (Svensson *et al*., 2004; Saely *et al.*, 2004) [32, 33]. Type 2 DM caries a high risk of large vessel atherosclerosis which is associated with hypertension, hyperlipidaemia and obesity. Most patients with type 2 diabetes die from cardiovascular complications and end stage renal disease (Bastaki *et al.*, 2005) [34].

**Pathological pathways involved in diabetes**

There are four key metabolic pathways playing major role in hyperglycaemia-induced cell damage and diabetes associated complications such as

(a) increased polyol pathway flux;

(b) increased advanced glycation end product (AGE) formation;

(c) activation of protein kinase C and

(d) increased hexosamine pathway flux (Robertson, 1995) [30]

In diabetes, cell damages are manifested through damage to proteins, lipids and carbohydrates, while the diabetic-associated complications include diabetic nephropathy, retinopathy, neuropathy, etc.

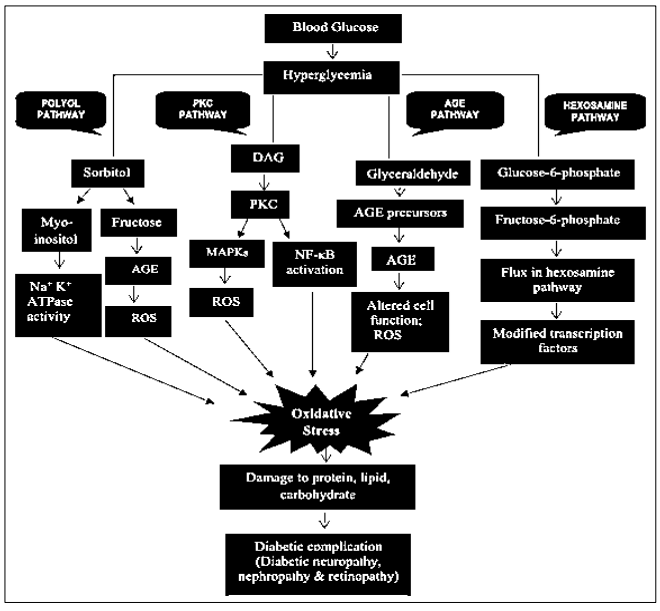


**Fig 2:** Hyperglycaemia-induced reactive oxygen species (ROS) generation and diabetic-associated pathological complications. ↑: Stimulate↓: Inhibit (Swagat *et al.*, 2016) [35]

**Role of insulin in diabetes mellitus**

Insulin is a polypeptide hormone synthesized in humans and

other mammals within the beta cells of the islets of Langerhans in the pancreas. The islets of Langerhans form the endocrine part of pancreas, accounting for 2% of the total mass of the pancreas, with beta cells constituting 60-80% of all the cells of islets of Langerhans (Anon, 2004) [36]. Insulin keeps a number of effects in many tissues, with liver, muscle, and adipose tissue as its important target organs. The basic physiological function of insulin is promoting the synthesis of carbohydrates, proteins, lipids, and nucleic acids. The effects of insulin on carbohydrate metabolism are like stimulation of glucose transport across muscle and adipocyte cell membranes, regulation of hepatic glycogen synthesis, and inhibition of glycogenolysis and gluconeogenesis (Piero, 2006) [24]. The end result of these actions is a reduction in blood glucose concentration. In case of protein metabolism, insulin promotes transfer of amino acids across membranes, stimulates protein synthesis, and also inhibits proteolysis. Incorporation of fatty acids from circulating triglyceride into adipose triglyceride and lipid synthesis are stimulated by insulin; lipolysis is inhibited. Insulin also plays role in nucleic acid synthesis by stimulating the formation of ATP, DNA, and RNA (Cahill, 1971) [37]. Insulin initiates its physiological effects by binding to a high affinity specific receptor located on the plasma membrane. The insulin receptor is saturable, and both the binding capacity and at a plasma insulin concentration of 20 to 30 µU/ml the binding capacity and biological activity are maximal. Insulin is not altered during the binding process, and reaction of the disulfide bonds is not involved. Upon binding to the receptor, insulin transmits its signal to the interior of the cell using a second messenger to influence enzymatic processes. By this way, insulin probably carries out its actions without entering the cell (Kibiti, 2006) [25]. Two membrane-bound enzyme systems are involved in the insulin signal: the adenyl cyclase- cAMP and the Magnesium - activated Sodium- Potassium- ATPase systems. Insulin inhibits cAMP formation only in situations where it has been previously stimulated by catecholamines, glucagons, or other hormones. Insulin also stimulates intracellular Potassium transport (Steiner, 1977) [38]. In turn, potassium is an important factor in membrane potential and enzymatic regulation. Magnesium is involved in the activation of many intracellular enzymes. Intracellular Magnesium accumulation is also promoted by insulin. It has been proposed that the insulin membrane receptor is located in the vicinity of the Magnesium-dependent Sodium-Potassium-ATPase system and that activation of the receptor modifies the activity of this system. This accumulation of intracellular magnesium causes activation of critical intracellular enzymes. After an overnight fast, the 8.00 am normal plasma insulin concentration ranges from 5 to 15 µU/ml. Postprandial values, 100g glucose can be 5 to 10 times higher than the baseline. Insulin output under basal condition approximates 0.5 to 1.0 U/h and increases about 5 times after food ingestion (Steiner, 1977) [38]. Mediating tissue glucose uptake by insulin is an important step in glucose homeostasis and to clear the postprandial glucose load (Reaven, 1983) [39]. The insulin production is directly proportional to the amount of sugar (carbohydrate) consumed. In case of more sugar consumption, the body will have to produce more insulin. But the tiny pancreatic beta cells cannot produce this required level of insulin. Because of a limited capacity to produce insulin, the forced over-production of insulin will eventually exhaust that capacity and the cells will cease to operate (Robert, 2002) [40]. However, blood glucose levels always do not act as the regulatory factor for insulin production and insulin is stored in cells before its release. Insulin is the major hormone that enables muscle and fat cells to uptake glucose from the bloodstream. Insulin causes most body tissues to remove glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage in body. Besides, insulin acts as the major regulatory signal for glycogenesis in the hepatocytes and myocytes (WHO, 1999) [41]. Higher insulin levels cause upregulation of various anabolic processes including cell growth, cellular protein synthesis, and fat storage. Insulin is more of an anabolic hormone rather than catabolic. Scantiness of insulin or poor cellular response to insulin and defective insulin leads to improper handling of glucose by body cells. This also leads to improper glucose storage in the liver and muscles which eventually leads to persistently high levels of blood glucose, poor protein synthesis, and different metabolic derangements (WHO, 1999) [41]. The chronic hyperglycemia arising from diabetes mellitus accompanies long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Autoimmune destruction of the pancreatic beta cells leads to insulin deficiency and bio-signalling derangements. These are consequent to insulin resistance or insensitivity. Defective insulin secretion and defective insulin action frequently coexist in the same patient. In type 2 diabetes mellitus, postabsorptive hepatic glucose production is increased and it is correlated with fasting plasma glucose concentration. In type 2 diabetes mellitus, gluconeogenesis drastically increases rather than glycogenolysis (Consoli, 1992) [42]. This enhanced release of gluconeogenic precursors causes increased total glucose output. But this unnecessary gluconeogenesis can be improved by inhibition of glycogenolysis and/or gluconeogenesis from endogenous precursors. Stimulation of intrahepatic disposal of neoformed glucose contributes to autoregulation. According to Tappy (1995) [43], intrahepatic disposal of glucose-6-phosphate plays a major role in the control of endogenous glucose production. Studies by Kahn and Porte (1988) [28], established that the degree of impaired beta-cell responsiveness to glucose is closely related to the degree of fasting hyperglycemia but in a curvilinear fashion. Decreased insulin secretion and defective cellular insulin action also compromises efficient glucose uptake by peripheral tissues. This derangement gets more predominant as the islet dysfunction declines. Halter *et al.* (1985) [44] argue that even if fasting insulin levels are comparable between type 2 diabetics and normal subjects, insulin secretion is markedly impaired in type 2 diabetics in relation to the degree of hyperglycemia present. Furthermore, in a noninsulin-dependent diabetes mellitus the extent of fasting hyperglycemia patient is closely related to the degree of impaired pancreatic beta-cell responsiveness to glucose.

**Complications of diabetes mellitus**

The complications are far less common and less severe if the blood sugar levels have been well-controlled. According to Edwin and his colleague's, acute complications include diabetic ketoacidosis, non-ketotic hyperosmolar coma, and diabetic coma. In case of chronic complication, chronic elevation of fasting blood glucose level leads to damage of blood vessels (Edwin *et al*., 2008) [45]. This chronically elevated blood glucose levels lead to increased mitochondrial reactive oxygen species (ROS) production. This in turn activates a number of metabolic pathways whose end products leads to the development of long-term complication of diabetes (Weiss and Sumpio, 2006) [46]. These metabolic pathways are activated by hyperglycemia-induced ROS that

includes the polyol pathway, formation of AGE, hexosamine pathway and the protein kinase C (PKC) pathway as shown the figure 2 (Forbes and Cooper, 2013) [47]. In diabetes, the subsequent problems are grouped under "micro-vascular complication" due to damage to small blood vessels and "macro-vascular complication" due to damage of the arteries (ADA, 2011) [48]. Micro-vascular complications can lead to retinopathy, neuropathy and nephropathy. Macro-vascular complications can also lead to cardiovascular disease and atherosclerosis disorders namely: (1) Coronary artery disease, (2) Stroke (mainly ischemic type), (3) Peripheral vascular disease, which contributes to intermittent claudication (exertion-related foot pain) as well as diabetic foot (Edwin *et al*., 2008) [49].

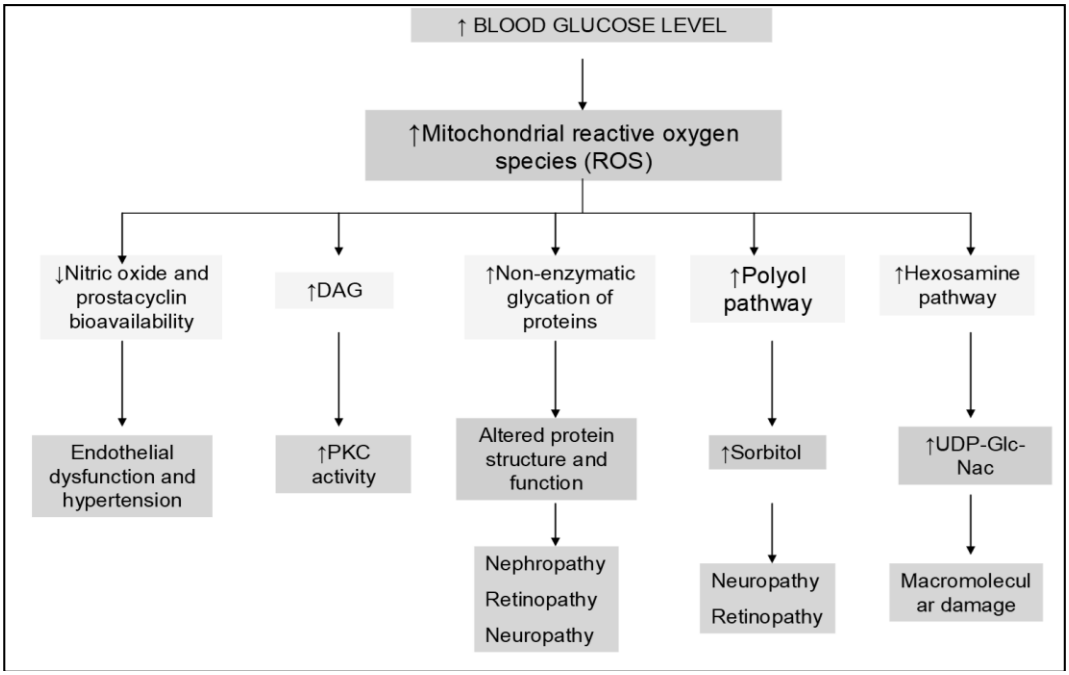


**Fig 3:** Metabolic pathways activated by chronically elevated blood glucose levels and long-term complications of diabetes mellitus, DAG- Diacylglycerol, PKC- protein Kinase C, Glc - Glucosamine, UDP- Uridine diphosphate, Nac- N- Acetylglucosamine (Weiss and Sumpio, 2006) [46]

**Diagnosis of diabetes mellitus**

According to the American Diabetes Association (ADA), the fasting glucose concentration should be used in routine screening for diabetes; but postprandial blood sugar, random blood sugar and glucose tolerance tests are also used for blood sugar determination. For the diagnosis of diabetes, at least one criterion must apply: Symptoms of diabetes (polyurea, polydipsia, unexplained weight loss, etc.) as well as casual plasma glucose concentration = 11.1 mmol/L (200 mg/dL). The normal range of fasting plasma glucose is 70-110 mg/dl with no caloric intake for at least 8 h. The World Health Organization (WHO) proposed classification that includes both clinical stages (normoglycaemia, impaired glucose tolerance/impaired fasting glucose (IGT/IFG), diabetes) and etiological types of diabetes mellitus, identical to the ADA except that WHO group includes classification formerly known as gestational impaired glucose tolerance (GIGT) and GDM: fasting glucose = 7.0 mmol/L (126 mg/dL) and/or 2-h glucose = 7.8 mmol/L (140 mg/dL) after a 75-g OGTT.

**Diagnostics tests for diabetes and prediabetes**

Popularly used diagnostic criteria for diabetes is below

**Random blood sugar test:** Randomly taken blood sugar level of 200 milligrams per deciliter (mg/dL)-11.1 millimoles per liter (mmol/L)-or higher suggests diabetes.

**Fasting blood sugar test:** An overnight fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level between 100 and 125 mg/dL (5.6 to 6.9 mmol/L) is determined as an indicator of prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests diabetes is confirmed.

**Oral glucose tolerance test:** Blood sugar level is measured after fasting overnight. Then blood sugar levels are tested periodically for the next two hours after consuming a sugary liquid. If blood sugar level is less than 140 mg/dL (7.8 mmol/L), it is normal. A reading of more than 200 mg/dL (11.1 mmol/L) after two hours is indicative of diabetes. A result between 140 and 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) indicates prediabetes.

If type 1 diabetes is suspicious, urine will be tested to find the presence of a byproduct produced when muscle and fat tissue are used for energy when the body doesn't have enough insulin to use the available glucose (ketones) (Mayo Clinic, 2014) [49].

**Management of diabetes mellitus**

**Goals of management**

Primary prevention is the main aim at preventing diabetes from occurring in susceptible individuals or in general population. Regular physical activity is an important component of the prevention and management of type 2 diabetes mellitus. According to Ross *et al.*, (2000) [50], increased physical activity, independently of other risk factors, has a protective effect against the development of type 2 diabetes. Dietary and lifestyle modifications are the main goals of treatment and management for type 2 diabetes. The majority of people with type 2 diabetes is overweight and usually has other metabolic disorders of the insulin resistance syndrome, so the major aims of dietary and lifestyle changes

are to reduce weight, improve glycemic control and reduce the risk of coronary heart disease (CHD), which accounts for 70% to 80% of deaths among those with diabetes (Bethesda, 1995) [51]. Insulin replacement therapy is the only option for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycemic agents are also useful in the treatment of type 2 DM. Available oral hypoglycemics include sulphonylureas, biguanides, alpha glucosidase inhibitors and thiazolidenediones. Their main goal is to restore normal metabolic disorder such as insulin resistance and inadequate insulin secretion from pancreas. Diet and lifestyle strategies are to reduce weight, improve glycemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes (Kumar *et al.*, 2002) [52].

**Life style management**

It is apparently the cornerstone of management of diabetes mellitus. Lifestyle modification programs have exhibited significant improvement of risk factors for diabetes; although, the effect on diabetes incidence has not been reported (Rebecca *et al.*, 2009) [53]. The dietary management of diabetes mellitus complementary to lifestyle management. In type 2 diabetes, the dietary objective is for improved glycemic and lipid levels and weight loss as appropriate (Piero *et al.*, 2006) [24]. Suggesting that majority of type 2 DM can be prevented by lifestyle modification. Patients with type 2 DM should receive a medical nutrition evaluation and their lifestyle recommendations should be tailored according to physical and functional ability.

**Pharmacological agents**

i). Biguanides: Metformin is the most commonly used Biguanide in overweight and obese patients which suppresses hepatic glucose production, increases insulin sensitivity, enhances glucose uptake by phosphorylating GLUT-enhancer factor, increases fatty acid oxidation, and decreases the absorption of glucose from the gastrointestinal tract (Collier *et al.*, 2006) [54] Research published in 2008 shows further mechanism of action of metformin as activation of AMP-activated protein kinase, an enzyme that plays a role in the expression of hepatic gluconeogenic genes. Due to the concern of development of lactic acidosis, metformin should be used with caution in elderly diabetic individuals with renal impairment. It has a low incidence of hypoglycemia compared to sulfonylureas (Collier *et al.*, 2006) [54].

ii). Sulfonylureas: These are generally well tolerated but because they stimulate endogenous insulin secretion, they carry a risk of hypoglycemia (Chiniwala and Jabbour, 2011) [55]. Elderly patients, with DM who are treated with sulfonylureas have a 36% increased risk of hypoglycemia compared to younger patients (Staa *et al.*, 1997) [56]. Glyburide is associated with higher rates of hypoglycemia compared to glipizide (Shorr *et al.*, 1996) [57]. Some age-related risk factors of hyperglycemia are impaired renal function, simultaneous use of insulin or insulin sensitizers, age greater than 60 years, recent hospital discharge, alcohol abuse, caloric restriction, multiple medications or medications that potentiate sulfonylurea actions (Scheen, 2005) [58]. Use of long acting sulfonylurea such as glyburide should be avoided in elderly patients with DM and use of short-acting glipizide should be preferred (Chiniwala and Jabbour, 2011) [55].

iii). Meglitinides: Repaglinide and nateglinide are non-sulfonylurea secretagogues which act on the ATP-dependent K-channel in the pancreatic beta cells thereby stimulating the release of insulin from the beta cells, similar to sulfonylurea, though the binding site is different (Fuhlendorff *et al.*, 1998) [59]. Meglitinides exhibit a rapid onset and a short duration of action (4-6 hrs) and thus lower risk of hypoglycemia. These agents are given before meals for postprandial blood glucose control. Preprandial administration allows flexibility in case a meal is missed without increased risk of hypoglycemia (Blicklé, 2006) [60]. Repaglinide is mainly metabolized in the liver with very minimal amounts excreted via the kidneys and thus dose adjustment is not necessary in patients with renal insufficiency except those with end-stage renal disease (Fuhlendorff *et al.*, 1998) [59].

iv). Thiazolidinediones: Thiazolidinedione is an insulin sensitizer, selective ligands transcription factor peroxisomes proliferator-activated gamma. They are the first drugs to address the basic problem of insulin resistance in type 2 DM patients (Yki-jarvinen, 2004) [61] whose class now includes mainly pioglitazone after the restricted use of rosiglitazone recommended by Food and Drug Administration (FDA) recently due to increased cardiovascular events reported with rosiglitazone. Pioglitazone use is not associated with hypoglycemia and can be used in cases of renal impairment and thus well tolerated in older adults. On the other hand, due to concerns regarding peripheral edema, fluid retention and fracture risk in women, its use can be limited in older adults with DM. Pioglitazone should be avoided in elderly patients with congestive heart failure and is contraindicated in patients with class III-IV heart failure (Coniff *et al.*, 1995) [62].

v). Alpha-Glucosidase Inhibitors: Acarbose, Voglibose and Miglitol have not widely been used to treat type 2 DM individuals but are likely to be safe and effective. These agents are most effective for postprandial hyperglycemia and should be avoided in patients with significant renal impairment. Their use is usually limited due to high rates of side-effects such as diarrhoea and flatulence (Chiniwala *et al.*, 2011) [55]. Voglibose, the newest of this class, has been shown significantly improved glucose tolerance, in terms of delayed disease progression and in the number of patients who achieved normoglycemia (Kawamori *et al.*, 2009) [63].

vi). Incretin-Based Therapies: Glucagon-like peptide 1 (GLP-1) analogues are the foundation of incretin-based therapies which are to target this previously unrecognized feature of DM pathophysiology resulting in sustained improvements in glycemic control and improved body weight control (Stonehouse *et al.*, 2011) [64]. They are available for use as monotherapy, as an adjunct to diet and exercise or in combination with oral hypoglycemic agents in adults with type 2 DM. Examples are Exenatide, an incretin mimetic, and Liraglutide (Chiniwala *et al.*, 2011) [55]. There is no risk of hypoglycemia with the use of GLP1 therapies (unless combined with insulin secretagogues). According to emerging evidence, incretin-based therapies may show a positive impact on inflammation, cardiovascular and hepatic health, sleep, and the central nervous system (Stonehouse *et al.*, 2011) [64].

vii). Dipeptidyl-Peptidase IV Inhibitors: These agents inhibit dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme that rapidly inactivates both GLP-1 and GIP, increase active levels of these hormones and, in doing so, improves islet function and glycemic control in type 2 DM (Pratley *et al.*, 2007) [65]. This new class of anti-diabetogenic drugs provides

comparable efficacy to current treatments. This drugs are well tolerated, carry a low risk of hypoglycemia and are weight neutral. However, they are relatively expensive (Pratley and Salsali, 2007) [65]. The long-term durability of effect on glycemic control and beta-cell morphology and function remain to be established (Pratley *et al.*, 2007) [65].

viii). Insulin: Insulin is used alone or in combination with oral hypoglycemic agents. Basal insulin provides beneficial augmentation therapy if some beta cell function remains. Replacement of basal-bolus insulin is required is case of beta cell exhaustion. Rescue therapy using replacement is necessary in cases of glucose toxicity which should mimic the normal release of insulin by the beta cells of the pancreas (Mayfield *et al.*, 2004) [66] Insulin comes in injectable forms - rapid acting, short acting, intermediate acting and long acting. The long acting forms are cause lesser extent of hypoglycemia compared to the short acting forms.

ix). Insulin analogues: Insulin therapy was limited in its ability to mimic normal physiologic insulin secretion. Traditional intermediate- and long acting insulins (NPH insulin, lente insulin, and ultralente insulin) are limited by inconsistent absorption and peaks of action that may result in hypoglycemia (Burge and Schade, 1997; Cameron and Bennett, 2009) [67, 68]. The pharmacokinetic profiles of the new insulin analogues are distinct from those of the regular insulins, and their onset and durations of action range from rapid to prolonged. Currently, two rapid-acting insulin analogues, insulin lispro and insulin aspart, and one long-acting insulin analogue, insulin glargine, are available (Burge and Schade, 1997; Cameron and Bennett, 2009) [67, 68]

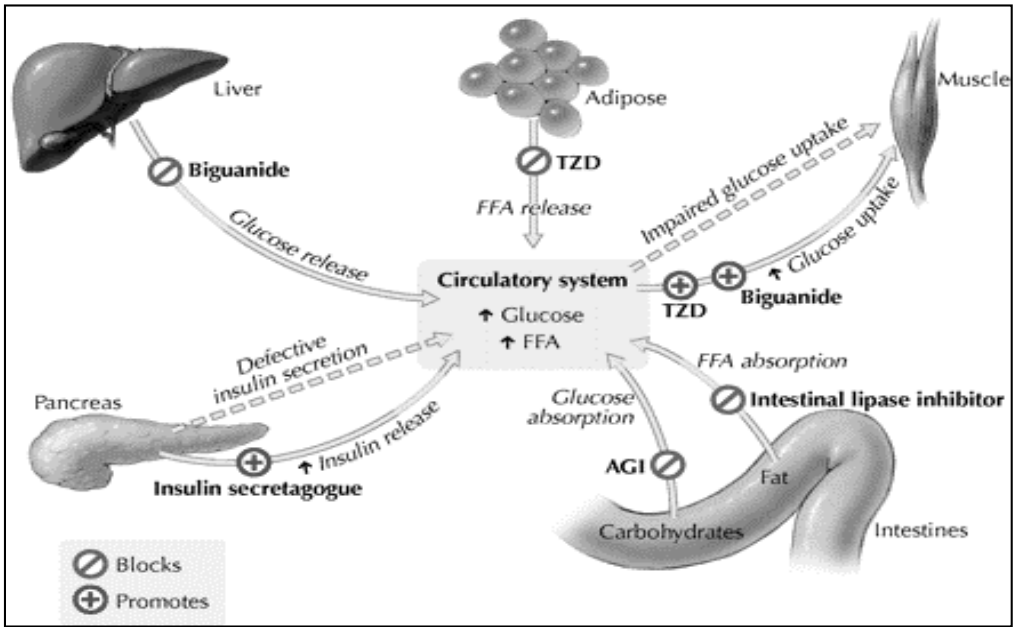


**Fig 4:** Major target organs and actions of orally administered antihyperglycemic agents in type 2 diabetes mellitus. Abbreviations: TZD = thiazolidinedione; FFA = free fatty acid; AGI = alpha glucosidase inhibitor (Cheng and Funtus, 2005) [69]

## Conclusion

Diabetes mellitus, a combination of several different metabolic disorders, if left untreated, causes abnormally high concentration glucose in the blood. Diabetes mellitus type 1 develops when the pancreas no longer produces significant amounts of the hormone insulin due to the autoimmune destruction of the insulin-producing beta cells of the pancreas. On the other hand, Diabetes mellitus type 2 is thought to result from autoimmune attacks on the pancreas and/or insulin resistance. The pancreas of a type 2 diabetic individual may be producing normal or even abnormally excessive amounts of insulin. The main goal of diabetes management mainly focuses to restore carbohydrate metabolism to a normal state. To achieve this goal, individuals with an absolute deficiency of insulin require insulin replacement therapy in the form of injectables or tablets. In contrast, dietary modifications and exercise can correct insulin resistance. Other goals of diabetes management are to prevent or treat the many complications arising from diabetes and to make its treatment safe. By maintaining a controlled the blood sugar, diabetes cannot prevent a patient from enjoying a joyful life.

## Conflict of interests

The authors have no conflicts of interests.

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