

# Schematic Review on Secondary Complications of Diabetes Mellitus

Pasupuleti Kishore Kumar<sup>1\*</sup>; Methuku Venu<sup>2</sup>; Adere Sushma<sup>3</sup>; Errolla Sneha<sup>4</sup>; T. Rama Rao<sup>5</sup>  
CMR College of Pharmacy, Kandlakoya, Hyderabad-501401, Telangana, India

Corresponding Author:- Dr. Pasupuleti Kishore Kumar<sup>1\*</sup>

**Abstract:-** “Diabetes Mellitus” is a metabolic disorder that characterized by reducing (or) increasing the insulin production. Diabetes mellitus characterized by continual increase in blood sugar levels due to combination of insulin resistant & gradual decrease in insulin production. Diabetes is the fastest growing problem in the world, with more than 400 million of cases & it accounts for 65% of costs and hospitalization for 35%. An increase in diabetes mellitus in every year leads to increase in morbidity & mortality among the people. Beta cells of islets of Langerhans releases insulin. Diabetes is mainly two types - Type 1 & Type 2. Type 1 diabetes is also called as insulin dependent / juvenile diabetes, whereas the Type 2 diabetes is known as diabetes mellitus. Primary drivers of type-2 diabetes are genetics & lifestyle. Sedentary life-style is a major factor that plays an important role in the development of diabetes mellitus. Long term concerns about diabetes can be reduced by maintaining a good life-style, healthy food, proper medication. Improper management of diabetes will have an impact on quality of life of a patient. Long term complications of diabetes include heart disease, stroke, eye damage, foot pain. To overcome this problem general treatment involves like maintaining a healthy diet, quitting smoking, maintaining a normal body weight, and also including physical exercise.

**Keywords:-** Diabetes Mellitus, Type 1 & Type 2 Diabetes, Gestational Diabetes, Diabetic Ketoacidosis, Hypoglycaemia, Retinopathy, Nephropathy, Neuropathy, Dermopathy, Cardiovascular, Cerebrovascular, Peripheral Vascular Disease.

## I. INTRODUCTION

Diabetes mellitus is a chronic illness that causes increased food consumption, higher blood sugar levels, and high blood pressure due to poor (or) inadequate insulin responsiveness. Diabetes is a complex disease that can be caused by a number of different conditions and is defined by chronic hyperglycaemia. Long-term effects of diabetes mellitus include organ failure and dysfunction, including those of the blood vessels, kidneys, eyes, nerves, and kidneys [1]. Diabetes mellitus, a common endocrine condition, is commonly referred to as "sugar". It usually occurs when there is either too little or no insulin. Insulin is secreted by beta cells of the islets of Langerhans, and glucagon is secreted by alpha cells, both of which are found

in the pancreas. Diabetes is mostly regulated by insulin and glucagon. Glucagon increases blood sugar levels, but insulin decreases them by facilitating the transfer of glucose to the muscles, liver, and adipose tissue [2]. Although erythrocytes and muscle tissue may absorb glucose without the help of insulin, alpha cells are crucial for blood sugar regulation because they produce glucagon and encourage glycogenesis, which raises blood sugar levels [3].

Type 1 diabetes mellitus is an autoimmune disease, in which pancreas produce less or no insulin. It typically occurs in adolescence; Type 1 diabetes is also called as “juvenile diabetes”. The general treatment for type 1 diabetes involves insulin replacement therapy. Type 2 diabetes is characterized by resistance in insulin and impaired insulin production. Type 2 diabetes is also called as “adult-onset diabetes”, generally it can be treated by oral hypoglycaemic agents [4].

➤ *Types of Diabetes Mellitus: -*

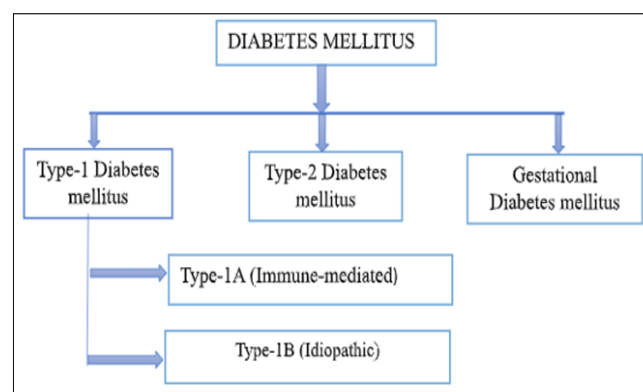


Fig 1 Flowchart Showing Types of Diabetes Mellitus

- Type 1A – in this type 1A diabetes mellitus, destroying of beta cells are mediated by immune system leads to insulin deficiency.
- Type 1B – there are no causes for insulin deficiency and no autoimmune mechanism involved in destruction of beta cells.

Gestational diabetes mellitus – it is a condition characterized by glucose intolerance (disglycemia). Improper production of insulin during pregnancy leads to gestational diabetes, people with this type of diabetes mellitus has a higher chance of getting type 2 diabetes mellitus [5].

**II. ETIOLOGY OF DIABETES MELLITUS**

The term "etiology" refers to potential origin and causes of the disease. It is currently thought that autoimmune causes contribute to type 1 diabetes mellitus. Viruses may be an important variable in the occurrence of diabetes mellitus. It is being proven that viruses like the mumps and rubella viruses cause morphological changes in human cell structure.

It is controversial that how much of diabetes mellitus' etiology is inherited, perhaps a person's genetic composition makes the pancreas accessible to one of the preceding viruses [2].

**A. Causes & Risk factors for Diabetes Mellitus: -**

A disorder in glucose cell receptors permits them to respond to high levels of glucose or beta cell depletion. Inadequate insulin production triggers beta cell death, which in turn induces hyperglycaemia, alterations in neuronal metabolism, and the concept that primary neuronal hypoxia results in micro vascular problems [6]. In cases of abdominal obesity, dyslipidaemia, and hyperinsulinemia with normal blood glucose levels, it declines the number of insulin receptors and triggers their down regulation, minimizing the sensitivity of peripheral tissue to insulin. As a result, the liver, muscle, and fat in specific areas suffer from insulin resistance. Various kinds of diabetes mellitus based on by particular genetic flaws [7].

**➤ Risk Factors for Type 1 DM:-**

It's regarded that immune system reactions lead to type 1 diabetes. Type 1 diabetes's risk factors include:

- **Family History: -**  
If diabetes appears in a family, it can have an impact on future generations via genetic. In addition, the primary risk factor for diabetes is family history. The risk can be even higher if both the mother and the father have diabetes.
- **Age: -**  
Type 1 diabetes is usually experienced by adolescents and young people. Type 1 diabetes may arise at any age; later onset diabetes is quite rare.
- **Genetics: -**  
Certain genes can raise the possibility of causing type 1 diabetes.

**➤ Risk Factors for Type 2 DM:-**

Type 2 diabetes is mostly develop if we have:-

- Over weight (obesity),
- Impaired glucose tolerance (pre-diabetes),
- Older age (usually people with age of 45 years),
- Genetic problem,
- Physically inactive.

Body Mass Index (BMI) is used to diagnose obesity; most persons with a BMI of 25 or more are regarded as overweight and at a high risk of type 2 diabetes. Men who

have a waist circumference greater than 40 inches and non-pregnant women who have a waist circumference more than 35 inches both have a higher chance of acquiring diabetes [8].

**➤ Risk Factors for Gestational DM: -**

This is usually occurring in women who are pregnant, in this condition their body unable to make insulin that leads to gestational diabetes. Some factors includes:

- Glucose intolerance during pregnancy,
- Hormonal disorder,
- Improper development of insulin during pregnancy,
- Having family history of type 2 diabetes, etc.

Elevated urine glucose is often cited as a risk factor, but is not considered a reliable indicator of gestational DM [9].

**• Signs & symptoms of Diabetes Mellitus: -**

Due to diabetes chronic nature, many people neglect to be paid attention to the disease's warning signs and symptoms. Because the signs of hyperglycaemia take time to appear, people may not consider it to be a serious problem. Some people are ignorant, that damage can start happening years before symptoms show up, and that early symptoms can help to control the disease immediately and minimize vascular problems [10].

**• Signs: -**

The signs of diabetes mellitus includes the following [11].

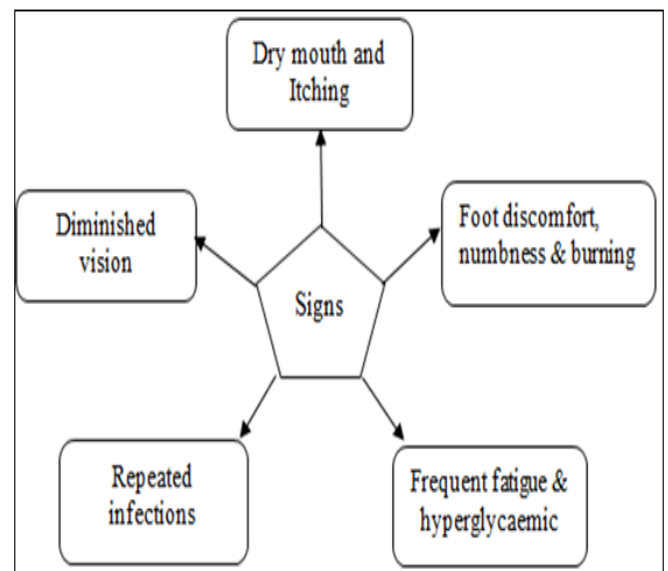


Fig 2 Signs

**• Symptoms:-**

Diabetes mellitus involves various number of symptoms, some of them includes [12]

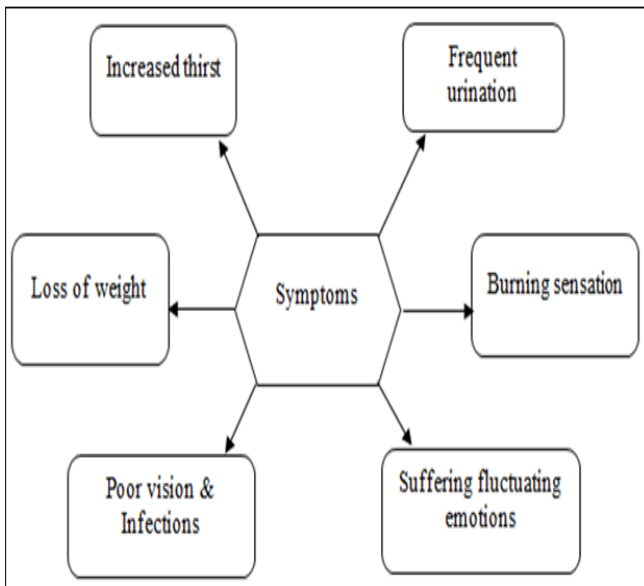


Fig 3 Symptoms

### B. Pathophysiology of Diabetes Mellitus: -

The pathophysiology of diabetes is a complicated procedure that depends on the interaction of growth factors, glucagon, and insulin in an accurate balance to regulate blood glucose levels, the progression of diabetes, and its consequences [13].

#### ➤ Type-1:

The immune system of the body incorrectly attacks and kills the insulin-producing pancreatic cells, resulting in type 1 diabetes, a chronic medical illness. A complicated interaction of hereditary and environmental variables causes this autoimmune reaction [14].

Insulin-producing cells are lacking in the pancreas, and the CD4+CD8+T cells that are still present are not capable of regenerating. Along a reduction in the production of insulin, people with IDDM also have abnormal pancreatic -cell activity, that results in an excessive release of glucagon. Insulin dependent diabetes mellitus (IDDM) patients do not display the expected inhibition of glucagon production in response to high blood sugar levels. Instead, they continue to secrete glucagon as usual. Increased amounts of glucagon brought on by this illness increase metabolic imbalances, promote lipolysis, and raise blood levels of free fatty acids. Due to a lack of insulin, these high levels interfere with the metabolism of glucose in peripheral tissues such skeletal muscle. This affects how glucose is used, and insulin shortage causes several genes—including glucokinase—to express at lower levels than are essential for target tissues to respond to insulin normally. Lack of insulin promotes insufficient lipid, protein, and glucose metabolism in persons with Type 1 diabetes mellitus [15].

#### ➤ Type-2:

In pathogenesis of Type 2 diabetes mellitus, beta cell dysfunction, and insulin remaining complicated. Increasing insulin resistance and beta cell dysfunction can both result from the onset of hyperglycaemia. Insulin resistance is fairly mild compared to beta cell failure [16]. In

case of  $\beta$  - cell dysfunction, insulin secretion is reduced, limiting the body's capacity to maintain physiological glucose levels. Several mechanisms have been proposed, including increased non-esterified fatty acids, inflammatory cytokines, adipocytes, and mitochondrial dysfunction for insulin resistance, and glucotoxicity, lipotoxicity, and amyloid formation for  $\beta$ -cell dysfunction [17].

On the other hand, insulin resistance plays a role in decreased glucose absorption in adipose tissue, muscle, and the liver as well as increased glucose synthesis in the liver. Through a variety of inflammatory processes, such as increased free fatty acid (FFA) release and imbalanced adipocytes, adipose tissue encourages insulin resistance. Although all of these processes occur early in the pathogenic process and help to cause the disease to manifest, -cell dysfunction is typically more severe than insulin resistance. However, when both insulin resistance and -cell dysfunction are present, hyperglycaemia becomes more severe, promoting Type 2 diabetes mellitus [18].

### III. TREATMENT FOR DIABETES MELLITUS

Management of diabetes involves an understanding of the disease's pathophysiology. Due to there is a severe lack of secretions in type 1 diabetes mellitus, insulin therapy is the only affordable treatment. Despite its complexity, type 2 diabetes mellitus is often recognized in its early stages by insulin resistance. Later stages of insulin resistance endure, although the lack of insulin secretion is more noticeable. The patient's disease stage and personal characteristics will consequently determine the therapy regimen [19].

#### ➤ Pharmacological Treatment:

Pharmacological treatment for diabetes mellitus includes

##### • Insulin Therapy:

Insulin, which is produced by pancreas, facilitates in the use and storage of glucose. Blood glucose, or glycaemia, cannot be monitored by patients with diabetes. For certain diabetics, insulin therapy makes it possible to maintain blood sugar levels. Insulin is administered in two major ways: as a basal dose, which provides a constant amount of insulin throughout the day and night, and as a bolus dose, which is administered at mealtimes for helping in the absorption of more blood sugar into muscle and fat. There are several various kinds of insulin, including inhaled insulin, mixed insulin, rapid-acting insulin, short-acting insulin, intermediate-acting insulin, and long-acting insulin. A combination of one or more insulin types can help in blood sugar control [20].

##### • Different Insulin Delivery Methods:

##### ✓ Insulin Syringe: -

Syringe is utilized to inject insulin from an insulin vial using a needle, which is injected under skin.

✓ *Insulin Pump*: -

It is used to pump insulin through skin while being worn. A tiny slit is used to connect the pump with a small needle that is embedded in the skin.

✓ *Replaceable Needle*: -

They are used to fill prefilled insulin under the skin in disposable insulin pens. Insulin pen designs are flexible.

✓ *Insulin Powders*: -

These can be inhaled through a small device like an inhaler. It is employed as a meal starter.

✓ *Injection Port*: -

Injection port is connected to a short tube that is inserted into tissue beneath the skin. Insulin with fast action can administered through a tube using syringes or pen. It is possible to keep the same injection site for 3 days and then switched it for a different location [21].

✓ *Daily Monitoring & Life Style Changes*: -

Combining treatment with preventative measures, such as quitting off smoking, increasing regular exercise, and adopting a nutritious diet. When you have diabetes, your body maintains your blood sugar levels in major part through your diet. Diabetes can be somewhat prevented by engaging in physical activities like yoga and exercise [22].

✓ *Managing Your Carbohydrates*: -

It's crucial to maintain your blood sugar levels if you have type 1 diabetes. Your blood sugar levels will be stabilized more effectively if you eat meals like brown rice that contain slow-release carbohydrates. For people with diabetes mellitus, low-carbohydrate sources are generally a better option [23].

✓ *Regular Exercise*: -

This is a must preferable one for the persons who are suffering with diabetes mellitus. Exercises play a crucial role in managing body mass & sugar levels.

✓ *Quitting Off Smoking*: -

As a result, smoking makes your body less responsive to insulin, you must use more insulin to control your blood sugar levels. Diabetes problems are brought on by persistent hyperglycaemia [24].

• *Oral Medications*:-✓ *Metformin*:

It is often the first drug to treat type 2 diabetes. Usually it helps to maintain blood sugar level.

✓ *Sulfonylureas*:

This drug help your body to release more insulin. It include gliclazide (Amaryl), glipizide (glucotrol), & glyburide (diabeta, micronase).

✓ *Meglitinides*:

They help your body to produce more insulin & work faster than sulfonylureas. Ex: - Nateglinide (starlin), Repaglinide (prandin).

✓ *Thiazolidinedione's*:

They help your body to utilize more insulin, but it may increase the risk of heart problems. Ex: - Rosiglitazone (Avandia).

✓ *DPP-4 (Dipeptidyl Peptidase) Inhibitors*:

Helps to lower blood sugar, but they cause joint pain & irritate your pancreas. Ex: - sitagliptin, soxagliptine.

✓ *GLP-1 Receptor Agonists*:

This medication taken with a needle to slow digestion & lowers blood sugar. Ex: - Liraglutide (victoza), semaglutide (ozempic).

✓ *SGLT-2 (Sodium Glucose Cotransporter) Inhibitors*: -

They help your kidney filter out more glucose. Ex: - Bexagliflozin (Brenzavvy), Cangliflozin (Invokana) [25].

✓ *Non-Pharmacological Treatment*:

Medical nutrition therapy (MNT), weight management, physical activity, smoking cessation & psychosocial care are essential to achieve treatment goals and improve quality of life.

✓ *Dietary Management*:

Encouraging adherence to a healthy diet can be one of the most difficult aspects of diabetes care. Consuming a low glycaemic index foods to improve postprandial glycaemic excursion. A low calorie, low carbohydrate diet for weight management & metabolic control [26].

✓ *Weight Management*:

Weight loss and control measures are important for diabetes persons who are obese. Insulin secretion with diabetes mellitus / newly diagnosed type 2 diabetes is not always successful in promoting diabetes remission. With a weight loss of 5%, positive results can be seen related to glycaemic control, lipids and blood pressure.

✓ *Physical Activity*:

People with type 1 diabetes are get more benefitted by increasing their physical activity. Adult with diabetes should considered – aerobic activity for 5-10 min/day, participate in resistance and flexibility training 2-3 sessions / week, and doing yoga for 5-10 min/day [27].

✓ *Stress Reduction*:

Stress causes a dramatic increase in hormones that raise blood sugar levels. Therefore, it is very important for us to control our mental and physical stress. It is good to do breathing exercises like pranayama to achieve peace. Moving with good friends & travelling may help to reduce stress.

✓ *Good Personal Hygiene:*

Since the risk of infection is high in diabetes, it is important to maintain a good personal hygiene.

✓ *Motivation:*

It is the role of family, friends, and health care providers to motivate the patients to manage and control diabetes & its co-existing problems [28].

#### IV. SECONDARY COMPLICATIONS OF DIABETES MELITUS

➤ *Acute Complications:*

- *Diabetic Ketoacidosis.*
- *Hypoglycaemia.*

➤ *Chronic complications:*

- *Micro-Vascular:*

- ✓ *Retinopathy*
- ✓ *Nephropathy*
- ✓ *Neuropathy*
- ✓ *Dermopathy*

- *Macro-Vascular :*

- ✓ *Cerebrovascular*
- ✓ *Cardiovascular*
- ✓ *Peripheral vascular diseases [29].*

“**Acute problems**” result from uncontrolled high blood sugars (hyperglycaemia) and low blood sugars (hypoglycaemia), which are brought on by a mismatch between the amount of insulin available and need.

- *Diabetic Ketoacidosis:*

A potentially life-threatening complication of diabetes, diabetic ketoacidosis is most frequently noticed in type 1 diabetic patients and very rarely in type 2 patients. It is an absolute or relative lack of insulin triggered by high blood sugar.

Diabetic ketoacidosis (DKA) can be caused through a number of diseases, including alcoholism, trauma, pulmonary embolism, and myocardial infarction. Drugs like thiazides, sympathomimetic agents, and corticosteroids can also cause Diabetic ketoacidosis to accumulate. The mortality rate for those with Diabetic ketoacidosis is greater than 5% for elderly people & varies by nation for children. Diabetic ketoacidosis is one of the diabetic complications that can be preventable.

In DKA, increased gluconeogenesis, rapid glycogenolysis, and decreased glucose utilization can result from inadequate amounts of insulin and counter-regulatory hormones. Ultimately, this will result in hyperglycaemia. Additionally, they cause the release of free fatty acids from adipose tissue into the bloodstream, which are then converted to ketone bodies via hepatic fatty acid oxidation,

causing ketonemia and metabolic acidosis. Leucocytosis develops in the majority of DKA patients. In general, it is manageable with the replacement of insulin and electrolytes [30].

- *Pathophysiology:*

Type 1 diabetes presents with a complete insulin deficiency that requires the breakdown of amino acids and triglycerides for energy sources. Insulin resistance occurs when physiological stress or drugs change the balance of insulin which often requires more than what is given. Lack of insulin causes uncontrolled ketosis which will often have negative regulatory effects. In addition, the use of glucose is harmful. This metabolic derangement results in ketosis, acidosis, and hyperglycaemia that characterize DKA. Recent evidence suggests that DKA is a severe inflammatory condition in which inflammatory cytokines (tumour necrosis factor- $\alpha$  and interleukin- $\beta$ ) are elevated. , -6 and -8), C-reactive protein, reactive oxygen species in lipid peroxidation [31].

- *Treatment:*

If you have DKA, you will be treated in the emergency room or admitted to the hospital. Your treatment may include:

- ✓ *Replace the fluids you lose through urine regularly and help keep your blood sugar stable.*
- ✓ *Replace electrolytes (minerals in your body that help your nerves, muscles, heart, and brain work properly). Too little insulin can lower your electrolyte levels. Get insulin. Insulin reverses the conditions that cause DKA.*
- ✓ *Taking medications for any disease that causes DKA, such as antibiotics for an infection [32].*

- *Hypoglycemia:*

Low blood sugar, also known as diabetic hypoglycaemia, is a complication of diabetes mellitus. Patients with type 1 diabetes mellitus are more likely to have it, followed by those with type 2 diabetes. In general, hypoglycaemia happens when a diabetic therapy fails to accurately meet the body's physiological requirements, resulting in a drop in blood sugar levels below normal. Any individual with diabetes who takes medication to reduce their blood glucose may experience diabetic hypoglycaemia. In persons with type 2 diabetes, sulfonylureas can also lead to hypoglycaemia. People with diabetes who are prefer a good diet, exercise, or insulin sensitizers rarely have severe hypoglycaemia. Hypoglycaemia is a serious medical emergency that needs to be diagnosed and treated right away in order to prevent organ and brain damage [33].

“**Chronic complications**” Diabetes is a disease in which there is too much glucose (a type of sugar) in the blood. Over time, high blood sugar levels can damage the body's tissues. Possible long-term effects include macrovascular and microvascular damage, which can lead to heart attacks, strokes, and problems with the kidneys, eyes, gums, feet, and nerves.

- *Micro-Vascular:*

- ✓ *Retinopathy:*

The most significant complication of diabetes mellitus (DM) is diabetic retinopathy (DR). It has long been understood to be a microvascular condition. A significant side effect of diabetes mellitus (DM), which continues to be a primary cause of vision loss in people of working age, is diabetic retinopathy (DR). Clinical signs of retinal vascular anomalies are used to make the diagnosis of DR. Non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) are the two clinical stages of Diabetic retinopathy. The early stage of Diabetic retinopathy is known as non-proliferative diabetic retinopathy (NPDR), and the retinal vasculature is characterized by increased vascular permeability and capillary blockage [34].

A condition of the retinal capillaries at first, diabetic retinopathy later spreads to the bigger arteries. Microaneurysm development, capillary leakage causing intraretinal haemorrhages, hard exudates, retinal edema, as well as capillary blockage causing ischemia and the production of cotton wool patches are all signs of microvascular lesions in the early stages of DR. Vascular alterations include vein bleeding, loop development, and intraretinal microvascular abnormalities (IRMA) are linked to more advanced stages of DR. The advancement of diabetic retinopathy (DR) results in neovascularization, intravitreal haemorrhages, increasing fibrous tissue, and traction and detachment of the retina. Any level of diabetic retinopathy may lead to exudative or ischemic types of the sight-threatening diabetic maculopathy [35].

- ✓ *Treatment:*

In the early stages of diabetic retinopathy, your eye doctor will only look at the condition of your eyes. Some people with diabetic retinopathy may need a dilated eye exam every 2 to 4 months. In other times, it is important to start treatment immediately, especially if your vision has changed. While it won't repair any damage to your vision, treatment can prevent your vision from getting worse. It is also important to take steps to control your diabetes, high blood pressure and cholesterol levels.

- *Injections:*

Drugs called anti-VEGF can reduce or reverse diabetic retinopathy. Other medications, called corticosteroids, can also help.

- *Laser Treatment:*

To reduce swelling in your retina, ophthalmologists can use lasers to slow down the blood vessels and stop them from dilating.

- *Eye Surgery:*

If the retina bleeds a lot or you have a lot of scarring in your eye, your eye doctor may recommend a type of surgery called a vitrectomy [36].

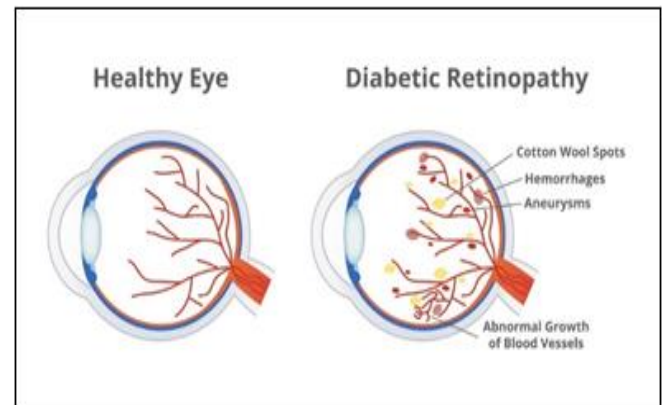


Fig 4 Diagram Showing Diabetic Retinopathy Condition [37]

- *Nephropathy:*

One of the main causes of death and morbidity in diabetic individuals is diabetic nephropathy (DN). In comparison to diabetic patients without nephropathy, those with diabetic nephropathy have a higher probability of death, mostly from cardiac issues. The main risk factors for the development of diabetic nephropathy are poor glycaemic control, long-term diabetes, insulin resistance, high blood pressure (BP), age, smoking, race, and genetic susceptibility. Diabetic nephropathy may also present as a falling estimated glomerular filtration rate with albuminuria as a minor presenting feature, especially in patients taking renin–angiotensin–aldosterone system inhibitors (RAAS). Renal disease in diabetic patients had been clinically characterized by increasing rates of urinary albumin excretion and decreasing renal function [38].

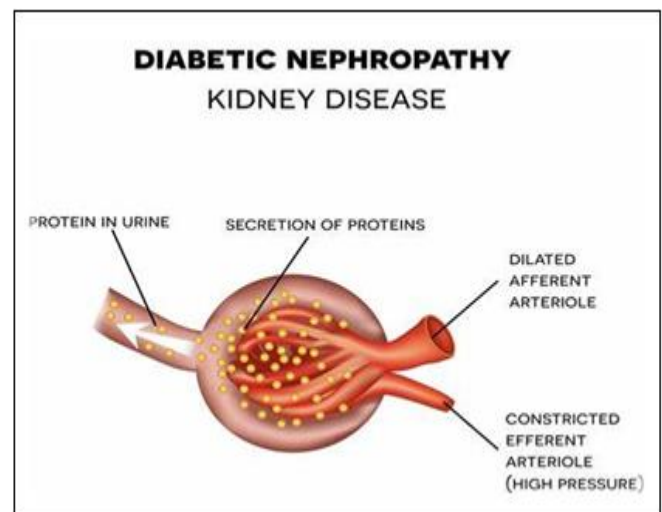


Fig 5 Diagram Showing the Nephropathy Condition in Diabetic Patients [39]

- *Treatment:*

There are several ways to treat diabetic nephropathy, including:

- ✓ Blood pressure regulation aids in kidney protection. BP needs to be kept at: 120–130 mm Hg for the systolic blood pressure & 70–80 mm Hg for diastolic blood pressure.

- ✓ Patients are given drugs like Angiotensin-converting enzyme (ACE) inhibitors because they are more effective at protecting kidney function than other blood pressure medications. Angiotensin-2 receptor blockers can be given to patients who are unable to tolerate ACE. Both of these drugs have the potential to result in hyperkalaemia, a state in which the blood potassium levels get elevated above normal.
- ✓ Medication-assisted cholesterol management is also essential.
- ✓ Renal Replacement Therapy (RRT) may be provided in the following ways after patients reach end-stage renal disease:
- ✓ Haemodialysis that uses filtration to remove hazardous substances from blood
- ✓ Wastes are eliminated through the abdominal cavity's lining membrane during peritoneal dialysis.
- ✓ Kidney transplantation for patients with total renal failure [40].

- *Neuropathy:*

Diabetes mellitus (DM) complications contain diabetic neuropathy (DN), a heterogeneous collection of severe or mild symptoms that damage the peripheral nervous system (PNS). Different pathophysiologic mechanisms, clinical manifestations, onsets, and evolutions are possible [41].

- *Types of Neuropathy:*

- ✓ *Peripheral Neuropathy:*

This type of neuropathic condition is also referred to as distal symmetric peripheral neuropathy. Diabetic neuropathy, which is the most common condition. Primarily to be affected are both hands, then foot and leg movement.

- ✓ *Autonomic Neuropathy:*

The autonomous nerve system regulates functions such as blood pressure, heart rate, body heat, eyes, bladder, digestion, and sex organs.

- ✓ *Diabetic Polyradiculopathy*, also known as proximal neuropathy, affects the nerves in the legs, thighs, hips, and buttocks.

- ✓ *Mono-Neuropathy:*

It is the condition where damages to a single nerve takes place. The nerve may be found in the arm, leg, torso, or face [42].

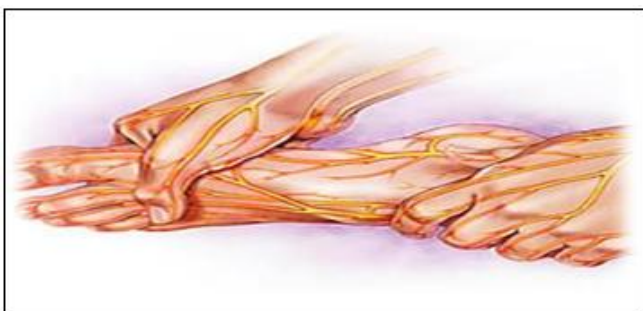


Fig 6 Diagram Showing the Condition of Neuropathy Patients with Diabetes [43].

- *Treatment:*

Through preventive treatment, neuropathy caused by diabetes and its related consequences can be avoided. Maintaining ideal glycaemic control can lower the incidence of peripheral neuropathy. For diabetics to avoid painless ulcers and bone infection, advice on proper foot hygiene, footwear, and hyposensitive region protection is required. Combining codeine phosphate with drugs like carbamazepine, phenytoin, or clonazepam can be advantageous. Tricyclic antidepressants, such as imipramine and amitriptyline, can be taken in doses ranging from 30 to 150 mg daily. Postural hypotension may be a possible side effect of tricyclic antidepressants. Additionally helpful are modern medications like pregabalin and duloxetine [44].

- *Dermopathy:*

Hans Melin originally noted diabetic dermopathy in 1964, and Binkley first used the term in 1965. The disorder was also referred to as spotted leg syndrome, diabetic dermopathy, darkened pretibial patches, diabetical dermangiopathy, and others [45]. Small, rounded, pink, reddish, or brown spots that form on your skin are a sign of dermopathy linked to diabetes. Scars and indentations may also be seen. They typically range in size from 1 to 2.5 cm. The patches do not itch, discharge any liquid, or provide any discomfort. The front of both lower legs, especially the shins, are usually affected by diabetes-related dermopathy, however one limb may have a lot patches than the other thighs and arms, as it can also appear on other body areas [46].



Fig 4 Condition of a Patient with Diabetic Dermopathy [47]

- *Treatment:*

Treatment is not necessary because diabetic dermopathy infections are asymptomatic and are known to go away on their own. New lesions develop as the previous ones disappear and infections normally suffer for 12 to 24 months. Haemoglobin (HbA1C) and diabetic dermopathy were also found to be unrelated, or to put it another way, managing glycaemic levels was discovered to have a varied effect on the improvement of skin lesions. The effectiveness of a product with modified collagen and glycerine lotion was studied in ten patients with Diabetic dermopathy in 2019 via support from Southwest Technologies. In addition, the lotion has resulted in beneficial results with no side effect [48].

- *Macro-Vascular:*

- *Cerebro-Vascular:*

Diabetic cerebrovascular conditions are characterized as cerebral small and big vessel diseases caused by cerebral vascular diseases brought on by diabetes with sugar, fat, and a number of nutritional substance abnormalities in the metabolism. Patients with type 2 diabetes who have cerebral blood vessel disorders make up 20% to 40% of the population. In patients with diabetes mellitus, diabetic cerebrovascular disorders are the leading causes of death. Acute cerebral vascular disease, stroke, cerebral small vessel disease, and asymptomatic cerebral atherosclerosis are the main clinical symptoms. The most serious side effects of diabetes, particularly in type 2 patients, are cerebrovascular disorders. Both ischemic stroke and haemorrhagic stroke are cerebrovascular disorders that can affect people with either macro-vascular disease or micro-vascular disease [49].

- *Treatment:*

There are three stages of therapy for people with Diabetes mellitus who have cerebrovascular diseases:

- ✓ The first level: lowering the risk factors brought on by hyperglycaemia, which can harm blood vessels, in patients who are at the stage of insulin resistance or early diabetes, in order to prevent issues involving the brain vessels.
- ✓ The second level: is to aggressively control hyperglycaemia after DM patients develop cerebrovascular illnesses. To prevent the vasculopathy-induced stroke, the blood pressure should be lowered back into the normal range.
- ✓ The third level: to enhance cerebral circulation, which could lower the death rate in DM patients following a stroke [50].

- *Cardio-Vascular:*

Diabetes increases your chance of developing heart disease. The condition, which is also known as cardiovascular disease, or coronary artery disease, can cause strokes and heart attacks. Your circulation is also impacted by cardiovascular disease. Additionally, other diabetes consequences, such as issues with your eyes and feet, are made worse by poor circulation.

Because of this, it's critical to look after your heart while you have diabetes. We're here to discuss why having diabetes raises your risk of developing cardiac issues and how you can lower that risk [51].

Since CVD is the more frequent cause of mortality and morbidity in DM patients, increasing the cardiovascular risks of diabetes patients must be the primary goal of care. However, the complex and persistent strength of the link between DM and CVD is a concern related to the management of DM and cardiovascular (CV) occurrences. Dyslipidaemia, hypertension, and obesity are common risk factors for cardiovascular in DM patients, especially those with type 2 DM. Numerous factors, such as neuropathy, endothelial dysfunction, coagulation enhancement, and an

increase in oxidative stress are usually present in diabetic individuals, which contributes to the development of CVD. When combined, increased risk factors for the cardiovascular system and the physiological effects of diabetes primarily on the cardiovascular system put diabetic patients at higher risk for developing chronic heart failure, stroke, revascularization, an increased risk of myocardial infarction, and other cardiovascular system disorders [52].

- *Treatment:*

Diabetes and cardiovascular illnesses require a multidisciplinary approach for optimal therapy. The cornerstone of this strategy is lifestyle changes, which include a balanced diet, exercise, weight loss, quitting smoking, and drinking less alcohol. Another concern is making sure people take their medications as prescribed. To improve results, specialists, primary care physicians, physical therapists, social workers, and educators about diet and diabetes should collaborate [53].

- *Peripheralvascular Disease (PVD):*

A common and serious consequence of diabetes mellitus is peripheral vascular disease. It has been well established that diabetic vasculopathy exhibits impaired collateralization, although its pathophysiology remains poorly understood. EPCs have recently been discovered to support angiogenesis and vascular healing. A lack of circulating Endothelial progenitor cells (EPC) have been linked to diabetes, however there is little information in the literature about the connection between EPCs and peripheral vascular disease (PVD) in diabetes [54].

Lower extremity atherosclerotic occlusive disease is known as peripheral artery disease (PAD). The risk of lower extremity amputation is enhanced by PAD, which is also an indicator for atherosclerosis in the cardiovascular, cerebral, and Reno-vascular systems. Therefore, patients with PAD have a higher risk of MI, stroke, and passing away. In addition, peripheral artery disease significantly impairs patients with diabetes over their lifetime. As a result of the requirement for numerous diagnostic tests, medical procedures, and hospital stays, managing people with peripheral artery disease can be costly [55].

## V. CONCLUSION

By reviewing the above article, we conclude that "Diabetes mellitus" is seen as a significant health issue that is expected to spread globally. The number of persons with diabetes mellitus is rising daily in developing countries, and complications may keep growing as well. Diabetes mellitus can cause a variety of secondary problems that have an effect on different organ systems and general health. Cardiovascular problems, neuropathy, nephropathy, retinopathy, and an elevated risk of infections are some of these side effects. Important steps in lowering the risk and severity of these consequences in people with diabetes include controlling blood sugar levels, maintaining a healthy lifestyle, and routine medical monitoring. Early detection and treatment are crucial to preventing or reducing the



consequences of these secondary complications and enhancing the quality of life for persons with diabetes.

### ACKNOWLEDGMENTS

I would like to express my profound gratitude to Mr. Dr. Pasupuleti Kishore kumar of Pharmacology department, and Mr. Dr. T. Rama Rao (Principal) of CMR college of Pharmacy for their contributions to the completion of my review article “Schematic review on secondary complications of diabetes mellitus”.

### REFERENCES

- [1]. Bhanoo Pratap Singh, Narjis fatma, Anil Kumar, Akanksha Sharma, Mansha. A Review on Diabetes Mellitus (DM); International Journal of Creative Research Thoughts [Internet]. 2022 May; 10 (5); page no: 1-2.
- [2]. Nishita Singh, Roohi Keshwani, Arun Kumar Tiwari and Dilip Kumar Patel. A Review on diabetes mellitus; The Pharma Innovation Journal [Internet]. 2016; 5 (7): 36-40.
- [3]. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *The Lancet* [Internet]. 2001 Jul; 358(9277):221–9.
- [4]. Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: a review on recent drug based therapeutics. *Biomedicine & Pharmacotherapy* [Internet]. 2020 Nov; 131:110708.
- [5]. Ng LC, Gupta M. Transdermal drug delivery systems in diabetes management: A review. *Asian Journal of Pharmaceutical Sciences*. 2020 Jan; 15(1):13.
- [6]. Singh CR. *Basic Pathology*, Prism PVT. Limited Bangalore, 2nd edition, 1992, 568-588.
- [7]. Ross and Wilson. *Pathophysiology in Health and Illness*, Churchill Livingstone Elsevier, 3rd edition, 2009, 215-220.
- [8]. Risk factors and diabetes: Type1 [Internet]. [www.medicalnewstoday.com](http://www.medicalnewstoday.com). Available from: <https://www.medicalnewstoday.com/articles/317168>.
- [9]. Li G, Wei T, Ni W, Zhang A, Zhang J, Xing Y, et al. Incidence and Risk Factors of Gestational Diabetes Mellitus: A Prospective Cohort Study in Qingdao, China. *Frontiers in Endocrinology*. 2020 Sep 11; 11.
- [10]. Ramachandran A. Know the signs and symptoms of diabetes. *The Indian Journal of Medical Research* [Internet]. 2014 Nov 1 [cited 2023 Sep 7]; 140(5):579–81.
- [11]. American Diabetes Association. Good to Know: Diabetes Symptoms and Tests. *Clinical Diabetes*. 2020 Jan; 38(1):108–8.
- [12]. Diabetes - Symptoms and causes [Internet]. Mayo Clinic. Available from: <https://www.mayoclinic.org/diseases-conditions/diabetes/symptoms-causes/syc-20371444>.
- [13]. Moini J. Pathophysiology of Diabetes. *Epidemiology of Diabetes* [Internet]. 2019; 25–43.
- [14]. Atkinson MA, Eisenbarth GS, Michel’s AW. Type 1 diabetes. *The Lancet* [Internet]. 2014 Jan; 383(9911):69–82.
- [15]. (PDF) The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus [Internet]. Research Gate. Available from: <https://www.researchgate.net/publication/312716171>
- [16]. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *The Lancet*. 2005 Apr; 365(9467):1333–46.
- [17]. Cerf ME. Beta Cell Dysfunction and Insulin Resistance. *Frontiers in Endocrinology* [Internet]. 2013; 4(37).
- [18]. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. *International Journal of Molecular Sciences* [Internet]. 2020 Aug 30; 21(17):1–34.
- [19]. Simó R, Hernández C. Treatment of Diabetes Mellitus: General Goals and Clinical Practice Management. *Revista Española de Cardiología (English Edition)* [Internet]. 2002 Aug 1; 55(8):845–60.
- [20]. JDRF. Treatments [Internet]. JDRF. 2019. Available from: <https://www.jdrf.org/t1d-resources/about/treatment/>.
- [21]. Diabetes - insulin therapy: MedlinePlus Medical Encyclopedia [Internet]. [Medlineplus.gov](http://medlineplus.gov). Available from:
- [22]. <https://medlineplus.gov/ency/patientinstructions/000965>.
- [23]. Lifestyle changes for Type 1 diabetes [Internet]. [www.diabeteswhatsnext.com](http://www.diabeteswhatsnext.com). Available from: <https://www.diabeteswhatsnext.com/global/en/about-diabetes/type-1-diabetes/lifestyle-changes-for-type-1-diabetes>.
- [24]. I have type 1 diabetes - what can I eat? [Internet]. Diabetes UK. Available from: <https://www.diabetes.org.uk/guide-to-diabetes/enjoy-food/eating-with-diabetes/i-have-type-1-diabetes>.
- [25]. Smoking and Diabetes [Internet]. My Type 1 Diabetes. Available from: <https://www.mytype1diabetes.nhs.uk/resources/internal/smoking-and-diabetes/>.
- [26]. WebMD. Type 2 Diabetes: The Basics [Internet]. WebMD. 2020. Available from: <https://www.webmd.com/diabetes/type-2-diabetes>.
- [27]. Raveendran AV. Non-pharmacological Treatment Options in the Management of Diabetes Mellitus. *European Endocrinology* [Internet]. 2018; 14(2):31.
- [28]. ADA. 5. Facilitating Behaviour Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes—2022. *Diabetes Care*. 2021 Dec 16; 45(Supplement\_1):S60–82.
- [29]. Non-pharmacological Management of Diabetes Mellitus! - By Dr. B Ramya [Internet]. Lybrate. Available from: <https://www.lybrate.com/topic/non-pharmacological-management-of-diabetes-mellitus>.

- [30]. Acute and chronic complications of DM [Internet]. www.slideshare.net. [cited 2023 Sep 13]. Available from: <https://www.slideshare.net/kapildev0034/acute-and-chronic-complications-of-dm>.
- [31]. Lizzo JM, Goyal A, Gupta V. Adult Diabetic Ketoacidosis [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2023 Jan.
- [32]. Dr. Kanuja Sood et al. Diabetes Ketoacidosis-Review article, Journal of cardiovascular disease Research (2023), 14 (4).
- [33]. CDC. Diabetic Ketoacidosis [Internet]. Centers for Disease Control and Prevention. 2021. Available from: <https://www.cdc.gov/diabetes/basics/diabetic-ketoacidosis>.
- [34]. Diabetic hypoglycaemia [Internet]. Wikipedia. 2023 [cited 2023 Sep 14]. Available from: [https://en.m.wikipedia.org/wiki/Diabetic\\_hypoglycaemia](https://en.m.wikipedia.org/wiki/Diabetic_hypoglycaemia).
- [35]. Wang W, Lo A. Diabetic Retinopathy: Pathophysiology and Treatments. International Journal of Molecular Sciences [Internet]. 2018 Jun 20; 19(6):1816
- [36]. Lobanovskaya N. Pathophysiology of Diabetic Retinopathy [Internet].
- [37]. Www.intechopen.com. Intech Open; 2022. Available from: <https://www.intechopen.com/chapters/79540>.
- [38]. National Eye Institute. Diabetic Retinopathy | National Eye Institute [Internet]. Nih.gov. 2019. Available from: <https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/diabetic-retinopathy>.
- [39]. Cdn-website.com. 2023 [cited 2023 Sep 14]. Available from: <https://irp.cdn-website.com/dd4586ba/dms3rep/multi/GettyImages-1364744625-b84f3d45.jpg>.
- [40]. Satirapoj B, Adler SG. Comprehensive approach to diabetic nephropathy. Kidney Research and Clinical Practice [Internet]. 2014 Sep 1 [cited 2020 Apr 24]; 33(3):121–31.
- [41]. Bing.com.2023.Availablefrom:<https://r.bing.com/rp/zYRmeqAE4Z0yDRz8nuL0syHMEI.svg>.
- [42]. Dr. Reeja Tharu. Treatment for Diabetic Kidney Disease [Internet]. Medindia. Medindia; 2014 [cited 2023 Sep 14]. Available from: <https://www.medindia.net/patients/patientinfo/diabetic-kidney-disease-treatment.htm>.
- [43]. Nascimento OJM do, Pupe CCB, Cavalcanti EBU. Diabetic neuropathy. Revista Dor [Internet]. 2016 [cited 2019 Nov 8]; 17.
- [44]. Mayo Clinic. Diabetic neuropathy - Symptoms and causes [Internet]. Mayo Clinic. 2022. Available from: <https://www.mayoclinic.org/diseases-conditions/diabetic-neuropathy/symptoms-causes/syc-20371580>.
- [45]. Pining.com. 2023 [cited 2023 Sep 14]. Available from: <https://i.pining.com/originals/ba/e7/43/bae743a5744c81389b9f72b255ead234.jpg>.
- [46]. Gerard said et.al. Diabetic Neuropathy-A Review. Nature clinical Practice Neurology. 2007 June; 3 (6): 331-340.
- [47]. Naik PP, Farrukh SN. Clinical Significance of Diabetic Dermatopathy. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy [Internet]. 2020 Dec 8 [cited 2021 May 26]; 13:4823–7.
- [48]. Diabetes-Related Dermopathy: Symptoms, Causes, and Treatment [Internet]. Cleveland Clinic. Available from: <https://my.clevelandclinic.org/health/diseases/22661-diabetic-dermatopathy>.
- [49]. Diabetes.co.in.2019[cited2023Sep14].Availablefrom: <https://diabetes.co.in/media/uploads/2020/06/diabetic-dermatopathy-pictures.jpg>.
- [50]. Google Scholar [Internet]. scholar.google.com. [cited 2023 Sep 14]. Available from: [https://scholar.google.com/scholar\\_lookup](https://scholar.google.com/scholar_lookup) (2003) vol; 69,105-108.
- [51]. Zhou H, Zhang X, Lu J. Progress on diabetic cerebrovascular diseases. Bosnian Journal of Basic Medical Sciences [Internet]. 2014 Nov 1 [cited 2023 Sep 14]; 14(4):185–90.
- [52]. Advieye Ergul, Aisha Kelly-Cobbs, et.al. Cerebrovascular complications of Diabetes: Focus on stroke. Google scholar [Internet]. 2012, vol: 12.
- [53]. Diabetes and heart disease [Internet]. Diabetes UK. Available from: [https://www.diabetes.org.uk/guide-to-diabetes/complications/cardiovascular\\_disease](https://www.diabetes.org.uk/guide-to-diabetes/complications/cardiovascular_disease).
- [54]. Sharma A, Mittal S, Aggarwal R, Chauhan MK. Diabetes and cardiovascular disease: inter-relation of risk factors and treatment. Future Journal of Pharmaceutical Sciences. 2020 Dec; 6(1).
- [55]. Ghimire B, Sakiewicz AJ. Management of Cardiovascular and Diabetes Risks Based On National Guidelines [Internet]. PubMed. Treasure Island (FL): Stat Pearls Publishing; 2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK580534/>.
- [56]. Google Scholar [Internet]. scholar.google.co.in. [cited 2023 Sep 14]. Available from: <https://scholar.google.co.in/scholar>.
- [57]. Thiruvoipati T. Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. World Journal of Diabetes [Internet]. 2015; 6(7):961.