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Diabetes Mellitus Disclosure: A Comprehensive Review on a Global Issue

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Abstract

Diabetes mellitus is a long-term metabolic disease associated with increased blood sugar levels that result from imperfections in insulin secretion. It is a genetic disorder that affects millions of people annually and inflicts substantial health threats. Various genetic and environmental factors play a significant role in the pathogenesis of diabetes. Type 1 diabetes is induced by an autoimmune reaction in the body that causes the deterioration of insulin-secreting cells in the pancreas. Whereas, Type 2 diabetes is a more severe form that is illustrated by the resistance and hindrance of insulin production. The contributing risk factors for diabetes comprise the genetic history of diabetes mellitus, overweight, poor way of living, and increasing age. The complexities linked with diabetes influence different organs by inducing heart disorders, nephrosis, retinal vascular disease, and peripheral neuropathy. Since diabetes mellitus is a chronic disease, it can develop the risk of other infections that affect the person's fitness. Management techniques for diabetes are important for keeping blood glucose levels in check. Insulin therapy, a healthy lifestyle, and proper exercise are crucial parameters to prevent diabetes mellitus. Some oral medications and injectable treatments aim to enhance the susceptibility, efficacy, and secretion of insulin to inhibit glucose assimilation. By comprehending the etiology and potential determinants, we can execute extensive management procedures to eliminate the soaring occurrence and problems analogous to diabetes mellitus. This review essentially highlights the essential factors linked with diabetes mellitus and useful management to improve the grade of life for people impacted by this chronic disease.

Keywords

Historical background of Diabetes, Types of Diabetes, Risk factors, Signs and symptoms, Prevention, Pathophysiology, Management, Treatment

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1. Introduction

Diabetes mellitus or simply diabetes is the most typical endocrine disease that influences nearly 100 million people around the globe. It affects almost 6% people of the total population annually. The depletion or improper insulin production by the pancreas provokes the onset of diabetes. The inadequate production of insulin mainly affects the glucose levels in the blood. As a result, it can damage many body systems including the vascular system, kidneys, eyes, and circulatory system (Ismail, 2009). Diabetes can be categorized into two types; Type 1 diabetes (insulin-dependent diabetes mellitus) and Type 2 diabetes (non-insulin-dependent diabetes mellitus). The causative agents and mode of action are different for both types of diabetes mellitus. Insulin-dependent diabetes is caused by inflammation in the region of islets of Langerhans that is pursued by the deterioration of insulin-producing cells. On the other hand, non-insulin-dependent diabetes mellitus is induced by the opposition of peripheral insulin and ineffective discharge of insulin (Arora et al., 2009). Besides Type 1 and Type 2 diabetes, another type of diabetes develops only in pregnant ladies called gestational diabetes mellitus and evolved after the beginning of the third trimester of gestation.

The history of diabetes is 3400 years old. In 1862, Ebers's papyrus was found in a grave in South Egypt. The body of papyrus contains various disorders and among them is a polyuric sickness, probably diabetes (Ebell, 1937). The Egyptians recommend that this malady can be dealt with by plant products. Some Indian researchers proposed that it can be genetic or occur later in life and is linked with ancestry, obesity, nutrition, and lifestyle (Algaonker, 1972). In the 5^{th} century before Christ, an Indian clinician Sushruta used the term “madhumeha” to indicate that the urine of a diabetic patient is not only sweet but feels gluey and can tempt ants. He was the first person who associate polyuria with sweet flavor stuff. He also pointed out that diabetes is linked to the excessive consumption of rice, grains, and confections (Peumery, 1987). The Greek investigators cited the symptoms of diabetes such as increased thirst, excessive urination, elevated blood glucose levels, and death. Aretaeus was a great physician who put forward the name diabetes in medical terminology. The work of Areateus is admirable because he talked about the clinical representation

and condition of patients with diabetes. Diabetes is a chronic and long-lasting disease where excessive drinking of water leads to polyuria and the patient feels pain and nausea. But if the patient doesn't drink water, he faces turmoil and a burning thirst (Laios et al., 2012; Adams, 1856).

Diabetes was previously regarded as a Western disease but now it has become a global threat (Wild et al., 2004). The International Diabetes Federation forecasted that there will be almost 390 million cases of diabetes by the year 2025. Around 80% of the disorder, the load is linked to developing and low-income countries (International Diabetes Federation 2006). Due to economic and nutritional problems, Asia has 60 % more cases of diabetes than any other continent. In China, the plurality of diabetes mellitus has elevated from 1% to 5.5% within 20 years (Gu et al., 2003). In 2006, the prevalence of Type 2 diabetes in rural regions of South India was nearly 9.3%, and it has inflated in urban areas of South India from 13.9%-18.6% from 2000 to 2006 (Ramachandran et al., 2008). In a survey, is proved that the highest rate of diabetes is present in India followed by Malaysia and China (Lee, 2000).

The risk factors of diabetes include: (i) Escalating abdominal obesity depends on the body mass index. Even with a lower body mass index, a person can develop diabetes (Yoon et al., 2006). If BMI≥25, then the person is overweight, and ≥ is for obese people. However, the data suggests that at a lower BMI, a person is at risk of acquiring type 2 diabetes (Huxley et al., 2008). (ii) Modifications and evolutions in nutrient intake and lifestyle may influence the onset of diabetes. Continuous socioeconomic transformations and rapid nutrition shifts are causing complications of malnutrition and overnutrition (Misra & Khurana., 2008; Siegel et al., 2008). (iii) Cigarette smoking can increase the risk of diabetes by 44% (Willi et al., 2007). (iv) Decreased function of pancreatic beta cells that are responsible for the production and secretion of insulin from the pancreas and (v) genetic variation is a major factor for diabetes. People with higher levels of glucose and lower insulin sensitivity are genetically more susceptible to diabetes (Dickinson et al., 2002). Other risk factors may be organic contaminants and environmental irritants like arsenic (Chen et al., 2007).

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Diabetes is a chronic disease with a slow progression. The signs and symptoms of this ailment are neglected because they do not show instantly. The manifestation of hyperglycemia is slow and, in the start, people are not aware of its devastation. The alarming signs and symptoms of diabetes are immediate weight loss, regular fatigue, nausea, crankiness, dryness in the mouth and eyes, burning sensation, pain, retardation in the recovery of wounds, and insensitivity in the feet. A diabetic patient may experience recounted infections of the urinary system, skin, oral fissure, and gonads. The common signs of Type 1 diabetes are excessive urination, excessive thirst, and undue eating along with weight loss. Type 2 diabetes is characterized by the demonstration of high levels of glucose in the blood, extreme weight loss, perturbation, and body aches. In 1997, the American Diabetes Association and the World Health Organization set the diagnostic concentration to a fasting plasma glucose level of 126 milligrams per deciliter (Gavin III et al., 1997; Alberti & Zimmet., 1998). Random plasma tests and oral glucose tolerance tests are also performed to diagnose diabetic patients. Pregnant women and infants are diagnosed by GDM screening tests. Another diagnostic technique used for diabetes is glycated hemoglobin. In 2011, the World Health Organization embraced glycated hemoglobin testing as a diagnostic test for diabetes (English & Lenters-Westra, 2018).

Primary and secondary preventions are designed to reduce the risk and prevalence of diabetes mellitus in a population. Diabetes can be prevented by a change in the behavior and way of living. It includes the consumption of a low-calorie diet, a balanced diet with essential nutrients, and regular physical exercise (NHLBI, 1998). As we know diabetes mellitus is a non-communicable disease and it can also be prevented by promoting education about diet, behavior, and lifestyle in organizations (Nader et al., 1999; Perry et al., 1998; Stone et al., 1996). The proper management and follow-up of diabetic patients are necessary to cope with the disease (UKPDS, 1998). Several researches have shown that strict metabolic management of glycemic can hinder the advancement of intricacies like nephropathy and retinopathy (ACCORD Study Group, 2010; Ismail Beigi et al., 2010; Shobana et al., 2005). To implement the management technique, the purpose is to diminish the substantial signs and prevent dehydration and secondary infections. For Type 1 diabetes,

effective blood glucose therapy is essential to control blood sugar levels with insulin, and for Type 2 diabetes insulin necessities can surpass 1 unit per kilogram per day (Hermansen et al., 2008).

Diabetes is a long-term chronic disease that needs to be managed properly. Besides management and control, some therapies and treatments are also available for diabetes mellitus. This includes traditional anti-diabetic medications that help in reducing the blood glucose levels to a normal capacity. These drugs help in the secretion and sensitivity of insulin from the pancreas and lessen the absorption of glucose in the intestine and tissues. Some anti-diabetic drugs are sulfonylureas, biguanides, thiazolidinediones, and acarbose (Modi, 2007). Moreover, some herbs are used as medicine to provide a safe mechanism for the management and prevention of diabetes mellitus. There are almost 800 plants are used for the supervision of diabetes mellitus but the entire mode of action is known only for 109 plants (Alarcon-Aguilara et al., 1998). Plants provide various benefits to deal with diabetes like the proliferation of beta cells, enhancement of insulin activity, maintaining carbohydrate metabolism, and useful antioxidant qualities. Some medicinal plants include *Panax ginseng* also called Korean red ginseng elevates the secretion of insulin to a level of 3.3mmol/liter (Kim & Kim., 2008). The carbohydrates, proteins, and peptides present in ginseng are beneficial in lowering glucose levels and creatinine concentration (Kimura et al., 1996). Another medicinal plant used for the treatment of diabetes is bitter melon (*Momordica charantia).* The curative substances found in bitter melon are charantin, vicine, antioxidants, and oleanolic acid glycosides. It induces glucose tolerance in Type 2 diabetes and STZ-induced cells prevent the suicidal death of beta cells by inflating glycogen concentration and excreting hexokinase and phosphofructokinase enzymes (Rathi et al., 2002). Other medicinal plants are *Coptis Chinensis* (Berberine), *Lagerstroemia Speciosa* (Banaba), Gymnema, Cassia cinnamon, and Agaricus mushroom.

2. Epidemiology of Diabetes

The survey on epidemiological data related to diabetes verified that there is a significant rise in the number of people living with diabetes accounting from 180 million diabetes cases in 1980 to more than 400 million cases in 2014 (Forouhi & Wareham, 2019). Obese people are at a high risk of

acquiring diabetes. Non-communicable diseases such as Diabetes have a maximal percentage (more than 50%) in developed states. The prevalence ratio for diabetes accounts for 7% and 13.7% in Africa and EMR (East Mediterranean regions) respectively (Roglic & Gojka.,2016). During 1900-1999; Finland, the UK, and Sweden areas showed the highest incidence rate of type-1 diabetes in children (Forouhi et al., 2010). According to 2023 data, smoking also serves as a risk factor for developing diabetes. 30-40% of type-2 diabetes can be reduced by discontinuing smoking. IDF (International Diabetes Federation) estimated an 8.8% diabetes prevalence in India (Kaur et al., 2018). In 2013, there were about >380 million cases of diabetes, and type-2 diabetes accounts for 95% of all diabetes cases. Aging, Hypertension, being overweight, high animal fat, and beverage consumption are the contributing factors to diabetes type-2 illness (Ma and Tong. 2024).

Globally, 422 million people are struggling with diabetes, and most of them belong to developing states. WHO data states that the rate of mortality for diabetes each year is nearly 1.5 million cases. The tragic loss of 2 million lives was reported in 2019 due to complications prompted by diabetes. Age-standardized prevalence shows an increase (approximately 3%) in fatality rate in the 21st century. In patients suffering from diabetes, cardiovascular illness reports > 80% of sudden death. In the US, diabetes incidence (type 2 diabetes) has risen tremendously, and around 20 million people are suffering from this disease. Population aging, obesity, physical inactivity together with sedentary lifestyle are the main reasons for the enhanced cases of diabetes (Winer et al., 2004). The number of diabetic patients has been rising over the past few decades. It is estimated that in the year 2050, the number of diabetic patients will grow to >48 million (Lin et al., 2018). By introducing effective interventions for individuals as well as the whole community, the disease burden of diabetes can be significantly reduced and promote the health of a vast global population (Deshpande et al., 2008).

3. Etiology and Risk Factors of Diabetes

Recent evidence on the etiology and pathogenicity of the diabetes mellitus has increased the heterogeneity of the disease. The only common factor to describe diabetes was abnormal glucose

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and there is disagreement on it at the National and International level (Alberti et al., 2006). A classification is made based on the insulin for research purposes. TYPE 1 diabetes includes insulin-dependent patients and TYPE 2 consists of non-insulin dependent patients. T1D is most commonly diagnosed in children with hyperglycemia. T2D is the common form of diabetes and is the cause of mortality worldwide. Type 2 disease is not a single disease but a collection of many disease syndromes. It reflects the genetic, pathological environmental, and metabolic irregularities in different patients. Multiple risk factors are involved in the onset of diabetes mellitus. It includes smoking, inadequate lifestyle, lack of physical exercise, and other environmental factors (Schulze et al., 2005). In obese people, the mass of adipose tissues increases, and dysregularity causes the onset of Type 2 Diabetes (Sears and Perry. 2015). Thus, obesity, urban dwelling, unhygienic diet, and old age are also a leading cause of diabetes. The prevalence of diabetes in Egypt is high and it also depends on socioeconomic status. Environmental factors also contribute to the T2D occurrence including air, food environmental walkability, etc. (Dendup, 2020). The effect of traffic noise is linked with high blood pressure and is seen in patients with poor sleep (Eze et al., 2017). Air pollution is also associated with Type 2 Diabetes. Higher air pollution triggers insulin resistance and is linked to obesity and hypertension (Brook et al., 2010).

4. Pathophysiology of Diabetes Mellitus

Pathophysiology means how illnesses or conditions impact the body's regular functions. Pathophysiology of diabetes means how diabetes can affect the body’s major organs and disturb the normal functioning of the body. A collection of illnesses diabetes mellitus is linked to elevated plasma glucose concentrations and abnormalities in glucose metabolism. Glucose is the main source of energy in the human body (Palicka, 2002). Diabetes comes in two prevalent forms: type 1 and type 2, which are brought on by intricate interactions between environmental variables and genetic predispositions. In Type 1 diabetes, insulin-producing cells are attacked by the immune system, which can be triggered by genetic factors. In Type 2 diabetes, insulin resistance and decreased function of β-cells are involved (Tesauro, 2002). In pancreatic beta cells, insulin first exists as a proinsulin precursor. Proinsulin is broken down into insulin and C-peptide as it is being

stored. These are kept in granules and are released in equimolar levels through exocytosis (Sherwin & Felig .,1978).

Type 1 diabetes mellitus is the result of a combination of genetic and environmental influences. Insulin-producing B-cells in the pancreas are most frequently destroyed by autoimmune diseases. According to Eisenbarth, intestinal viruses, food components, or environmental pollutants could all be responsible for the onset of T-cell-dependent autoimmunity (Barnette et Al., 2009). Major Histocompatibility (HLA) area has several hereditary locations, such as the alleles DR3/4, DQ 0201/0302, DR 4/4, and DQ 0300/0302 that are linked to an elevated probability to acquire type I DM. In cases where an immediate family member is afflicted, the probability of developing type 1 diabetes is about 5%; if the father is sick instead of the mother, the risk is slightly higher. Clinical experiments aimed at delaying or preventing type 1 diabetes in those with genetic susceptibility have not been successful thus far. Global research networks, such as TrialNet and TRIGR, are investigating methods to stop, slow down, or possibly reverse the course of type 1 diabetes (Wherrette & Daneman, 2009).

Type 2 diabetes is primarily caused by severe energy deficits in psychologically and epigenetically predisposed individuals (Colagiuri et Al., 2011). But many people who are severely malnourished, overweight, or obese either never acquire diabetes or acquire it very late in life. They are still able to withstand type 2 diabetes and can safely store excess calories in subcutaneous adipose tissue (SAT) as opposed towards the veins, muscles of the body. Due to different processes, including effective islet β-cell compensation, sustaining very similar blood nutrients, formation of reduced insulin intolerance, increased expansion of SAT relative to visceral adipose tissue (VAT), and inadequate rise in belly fat, the liver and islet β cells have both improved (Defronzo, 2009). This protects the body's vital organs from damage caused by nutrients. Type 2 diabetes develops in predisposed overfed persons because the fuel surplus could not be safely disposed of without these adaptive measures failing. Failure of islet β-cells to make up for energy excess, increased glucagon secretion and decreased incretin response, impaired SAT expansion, hypoadiponectinaemia, and adipose tissue inflammation, increased endogenous glucose production, and the emergence of peripheral insulin resistance are metabolic defects that are critical to the development of type 2

diabetes. It's significant that the fuel surplus needs to be disposed of somewhere else because it cannot be securely dumped into SAT. When the function of β-cells islet becomes worse, it requires insulin therapy (Weir et al., 2001).

Gestational Diabetes Mellitus is caused by a combination of insulin resistance and compromised beta cell activity. Reduced diabetic sensitivity is a hallmark of the diabetogenic condition of gestation. The onset of the second trimester of pregnancy is when this is most noticeable. Progesterone, cortisol, growth hormone, placental lactogen from humans, and prolactin are the main donors. Significant a lack of insulin results from these hormones' reduced activation of the insulin receptor target. Females who do not exhibit the normal features associated with an elevated risk of GDM, such as being slender and white people. Consequently, GDM is caused by the interaction of insulin intolerance and a hormonal malfunction during pregnancy (Friedman et al., 1999).

4.1. Effects of Diabetes on Eye:

For those over 50, diabetic retinopathy, or DR, is the most prevalent cause of blindness. Evidence that DR is an inflammatory illness is mounting. The eye is greatly affected by hyperglycemia. It results in diabetic keratopathy in the cornea and directly or indirectly destroys vascular and neuronal cells in the retina and choroid (Lutty, 2013). However, a hand-held ophthalmoscope can be used to directly observe the anatomical consequences of diabetes on the eye, particularly in the retina (Klein & Klein., 2013). Compared to patients without DM, those with DM without DR had a greater stray light level. Thus, the intraocular straylight level appeared to be influenced by the severity of DR. Even Nevertheless, there are no clear symptoms of DR (Hwang et al., 2015). The symptoms of diabetic corneal neuropathy include pain, ocular irritation, and photophobia. Damage to the cornea's tiny Aδ and C nerve fibers accounts for the bulk of corneal symptoms (Bikbova et al., 2018). Diabetic neuropathy may be caused by a variety of processes, including oxidative stress, signal pathways, and inflammation triggered by hyperglycemia. Hyperglycemia in diabetes mellitus results in the production of highly reactive metabolites called advanced glycation end-products, or AGEs, from the non-enzymatic glycosylation of carbohydrates that is simple sugar (Madonna et al., 2017). Innovative therapy modalities for diabetic keratopathy. More recently, it

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was shown that topical use of insulin, an opioid antagonist called naltrexone, and an ergoline derivative called nicergoline greatly improved and increased the rate of corneal wound healing (Abdelkader et al., 2013).

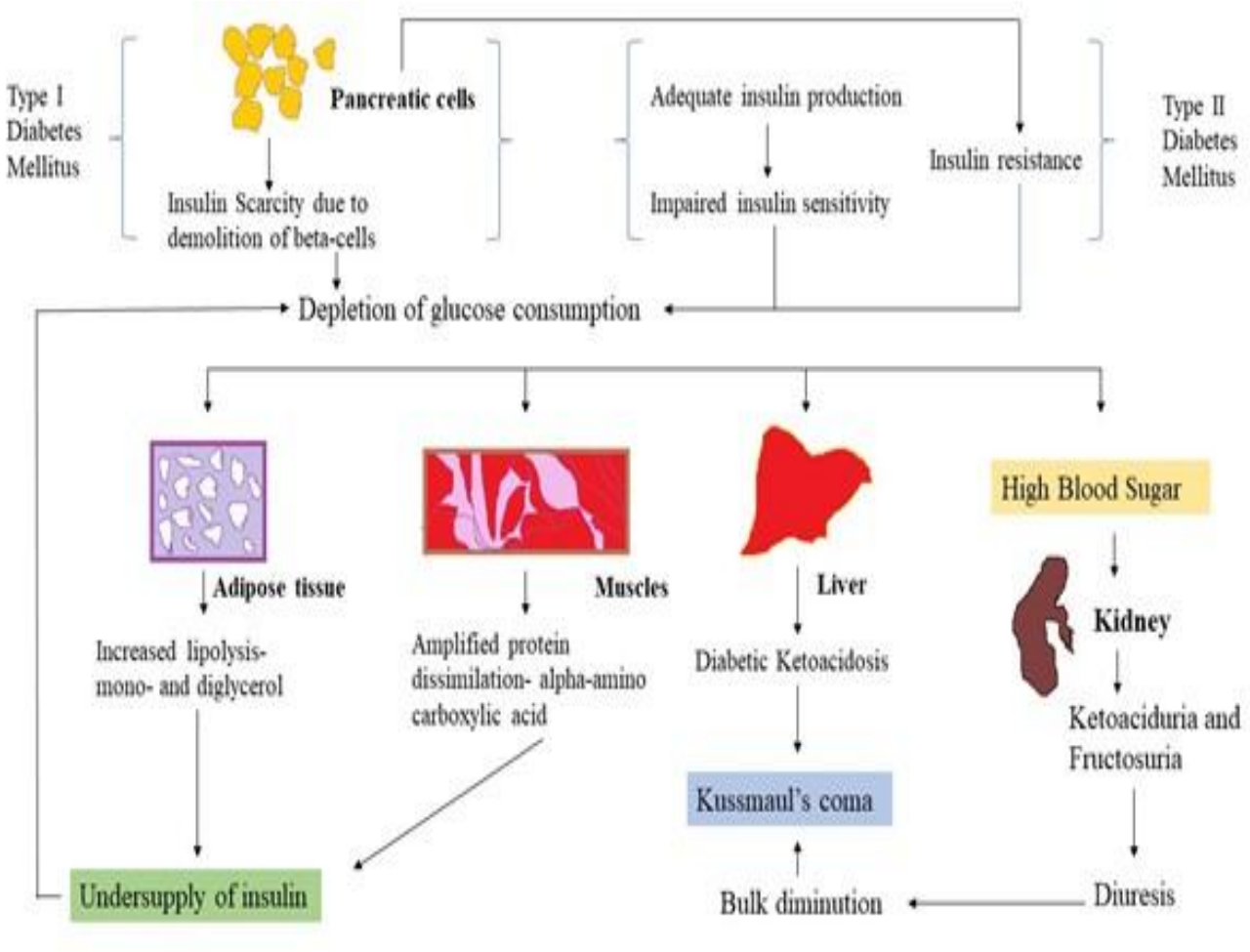

Fig 1: Pathophysiology of Diabetes Mellitus

5. Signs and Symptoms of Diabetes Mellitus:

The common symptoms of diabetes include excessive urination where the diabetic patients may urinate more than 2.5 liters a day, the feeling of dehydration and the urge to drink water, and the

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feeling of extreme hunger or bulimia nervosa along with tiredness and weakness (Baynes, 2022). In addition to the common symptoms of diabetes, men with diabetes may experience decreased sex drive, erectile dysfunction (ED), pruritus, and poor muscle strength (Rice et al., 2008). Women with diabetes may also have symptoms such as urinary tract infections, yeast infections, and dry itchy skin (Lima et al., 2017). Type 1 diabetes can include extreme hunger, increased thirst, unintentional weight loss, frequent urination, cloudy vision, tiredness, nighttime bed-wetting in children, and dehydration (Myers, 2014). It may also include a deficiency of minerals and water in the body and increased circulatory system disorders. Type 2 diabetes can include more hunger, wet mouth, excessive urination, blurred vision, fatigue, nausea, vomiting, chronic wounds, weight loss, frequent infection, headache, infection in gums, and tingling hands and feet (Ramaiah, 2002). It may also cause recurrent infections. This is because increased glucose levels make it difficult for the body to heal. Gestational diabetes may not have obvious signs or symptoms because many of the changes are similar to those that occur during pregnancy (Coustan, 2013). But common signs and symptoms are tiredness, weak vision, wet mouth, vomiting, excessive urination, vaginal, or skin infections, and glucose in urine (King & Thatcher, 1993). Any woman who has new or unusual symptoms during pregnancy should talk to her doctor.

6. Prevention of diabetes

Several studies suggest that an inactive lifestyle and less physical activity may disturb the normal glucose absorption in the blood leading to diabetes Type 2 and immature death in persons detected with diabetes (Albright et al., 2000; American Diabetes Association, 2004; Grundy et al., 2002; Redberg et al., 2002). Prevention is better than cure and diabetes is a long-term chronic disease that results in the death of the patient. Physical activity and wellness are the primary prevention of diabetes. They help reduce the signs, and symptoms and restrain the pathogenesis of the disease. Moreover, sufficient levels of cardiopulmonary soundness are also important in preventing diabetes. Type 2 diabetes mellitus is characterized by insulin opposition and deterioration of beta cells which varies among different people (Jensen et al., 2002; Weyer et al., 1999). Processes that inhibit insulin resistance and enhance beta cell functionality for insulin production are effective in preventing diabetes. Prevention measures for diabetic patients include weight control, adequate

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diet, exercise, surgeries, and medication (Norris et al., 2005). Metformin is a drug used for the deterrence of diabetes and 850mg of it is allotted to patients with inadequate glucose forbearance. It decreases the weight of a person by 1.7 kg and the prevalence of disease by 50%. Other medicines used for the prevention of diabetes are thiazolidinediones and acarbose. Acarbose is an alpha-glucosidase inhibitor that is used in clinical testing to prevent non-insulin-dependent diabetes mellitus (Yang et al., 2001; Holman et al., 2007; Pan et al., 2003).

Fig 2: Preventive measures and therapeutic strategies of Diabetes Mellitus

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7. Diagnosis of diabetes:

Diabetic and pre-diabetic patients are mostly recognized by screening that provides early management, possibly resulting in a low rate of future complications. The patients need to be examined with risk factors like hypertension, obesity, and family history of diabetes. Various tests are used to diagnose diabetes in different people. The diagnosis of diabetes mellitus mainly depends upon glucose level. The first expert committee on the diagnosis and classification of diabetes mellitus changed the diagnosis standard in 1997, according to which the glucose level has been recognized by the interrelation between FPG level and the appearance of retinopathy as a fundamental source. The threshold is 7 mmol/liter which means that is a level where the difficulties of diabetes and retinopathy can be diagnosed. However, in 1997, the criteria for diagnosis were the fasting glucose level of 110-125mg/dL (Gavin III et al., 1997). The American Diabetic Association lowered the fasting glucose level to 100-125mg/dL to evaluate the sensitivity of persons at risk of diabetes (Genuth et al., 2003). Various cross-sectional studies evaluated the glycemia as 2-h PG, FPG, and A1C. These studies also showed that the retinopathy increased above the glycemia level was related among the community. A1C is a mostly used glycemia test that helps in the administration of diabetic patients and is compatible with both microvascular and macrovascular problems (Qaseem et al., 2018). The FPG and 2-h PG tests include patients with severe hyperglycemia that are mostly diagnosed when a plasma level of $\geq$ 200 mg/dL (11.1 mmol/L) is developed. Type 1 and type 2 diabetes are also diagnosed by fasting plasma glucose test, random plasma test, and oral glucose tolerance test (Nichols et al., 2008). The fasting plasma glucose test needs eight hours of fasting before the test and more than 126 mg/dL glucose level indicates that the patients are diabetic. The random plasma test does not require fasting and patients with a blood glucose of more than 200 mg/dL showed a diagnosis of diabetes but are further confirmed (Alqahtani et al., 2013). The oral glucose tolerance test requires 8 to 16 hours of fasting and supplies 75 gm of glucose, 100 gm for pregnant women. A glucose level of less than 140 mg/dl within 2 hours is normal but a 2-hour glucose level of 200 mg/dL and fasting level of 160 mg/dL confirms the diagnosis of diabetes. The gestational diabetes mellitus (GDM) affects pregnant women and newborn infants and for its diagnosis, different criteria are used. One is 75g OOGT

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for 2 hours and the other one is 50g OOGT for 1 hour and eventually 100g OOGT for 3 hours (Adegbola & Ajayi, 2008). According to the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, the GDM prevalence increases from 5-6 to 15-20% which eventually results in diagnosis. In 2009, the International Expert Committee suggested researchers utilize the glycated

Hemoglobin test with an HbA1c level of 6.5% (Nathan et al., 2009). The American Diabetes Association (ADA) defines that the level of pre-diabetic glycated hemoglobin is 5.8-6.4% and individuals with a range of 6.0-6.4% are at risk of developing disease (Nathan et al., 2009); ADA,

Table 1: Significant Details of Different Types of Diabetes Mellitus

Types	Occurrence	Determinants	Clinical signs	Diagnosis	Associated problems	Control	Reference
Type I	6-11%	Hereditary, High blood pressure, Ecological	Polyuria, polydipsia, sudden weight loss, hyperphagia	Random blood sugar test, Fasting blood sugar test	Nephrosis, foot damage, eye complications, Heart problems	Screening of glucose levels, Exercise regularly, Consuming nutritious food	Karthikeyan, 2017
Type II	85-96%	Inactivity, Overweight, Cardiovascular disorders	Exhaustion, feeling thirsty, slow-healing wounds, cloudy vision	Hemoglobin A1c test, Plasma glucose aggregation (2-hour plasma glucose)	Cerebral stroke, Kidney disorders, Skin complications, Diabetic ketoacidosis	Weight maintenance, Utilization of diabetes drugs, Healthy diet	Alam, 2021

Gestational	Fluctuates	Polycystic ovary syndrome, Record of previous gestational diabetes	Increased birth weight, excessive urine production, candidiasis, nausea	Glucose challenge test, Oral glucose endurance test	Obesity, Abortion, Icterus, High blood pressure, Respiratory issues	Medicines to control blood sugar, Supervision of pregnancy, Ensure physical activity	Shwetha, 2019

8. Dietary Management for Diabetes Mellitus

A healthy diet is also an important part of good diabetes management (Sami et al., 2017). The goal is to help people with diabetes keep their blood sugar as close to normal as possi ble, achieve good blood lipid levels, maintain adult weight, and retain clean health by eating well and keeping the body strong. They include: (1) choose protein-rich food such as beans, fish, lean chicken, and lean meat (Wolfe et al., 2018). (2) Consume less oily foods such as whole grains, fruits, and vegetables (Liu, 2013). (3) get soluble fiber from oats, bran, dried peas, beans, cereals, and rice (Dreher, 2001). (4) Avoid fried foods, processed foods, and commercial baked goods (doughnuts, cookies, and crackers) (Oke et al., 2018). (5) Avoid eating animal products like eggs, cheese, milk, sugar, ice cream, and fatty meat (Teicholz, 2014). (6) Diabetics and people at high risk should not drink soda reduce the consumption of vegetable rice with added sugar to control weight, and reduce the risk of cardiovascular diseases and type B fatty liver because these foods can replace healthy and nutritious foods. Meat. (7) In patients with type 2 diabetes, eating protein appears to improve insulin response but does not increase blood sugar levels. Therefore, high-protein carbohydrate foods should be used to treat or prevent hypoglycemia. (8) Moderate weight loss achieved through a combination of calorie reduction and lifestyle changes may be effective in overweight or obese adults with type 2 diabetes and prediabetes (Lau & Teoh, 2013). (9) avoid the Western diet (Laing et al., 2019).

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8.1. Insulin Requirement for Diabetic Patients

A person with diabetes needs insulin depending on many factors, including blood sugar, diet, activity level, type of diabetes, and other conditions (Rahman et al., 2021). It is usually determined by a doctor who monitors insulin carefully and adjusts it as needed. The dose depends on your target blood sugar level, the amount of carbohydrates you eat, and how active you are. You can start with 4-6 units of insulin. Your dose will increase by 2-3 units every three days until you reach your blood sugar goals (Rothwell et al., 2010).

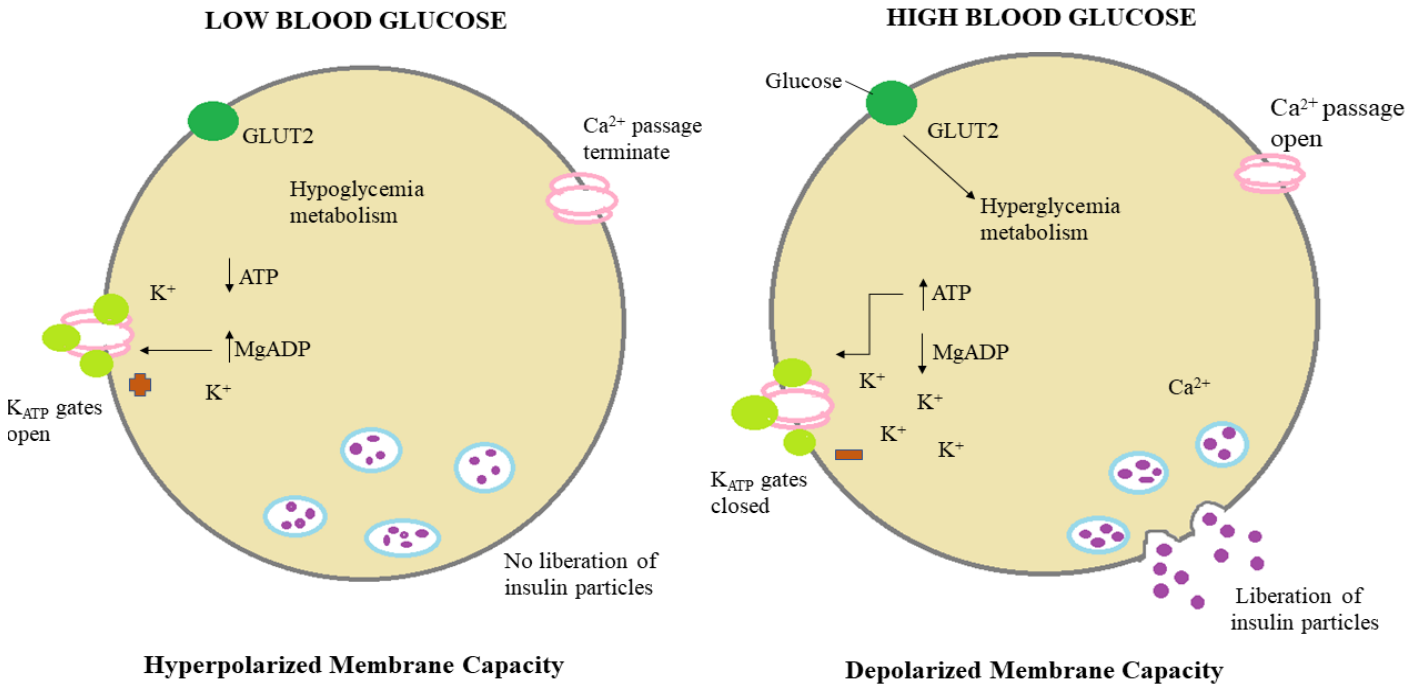

Fig 3: Glucose-triggered insulin production in beta cells of pancreas. When level of glucose is low in blood, then the reduced amount of the ratio ATP/Mg-ADP will stimulate the opening of KATP gates. As a result, the plasma membrane become hyperpolarized, deactivate the opening of calcium channels, calcium ions influx and insulin production (left). When glucose level decreases in blood, it is transferred to cell through GLUT2. Glucose digestion contribute to the elevated ratio of ATP/Mg-ATP, concluding in the termination of KATP gates, causing membrane to depolarize, opening of calcium channels, calcium invasion and insulin mission (right).

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9. Complications of Diabetes Mellitus (DM)

Diabetes is the root of numerous severe complications in patients suffering from diabetes mellitus, uncontrolled or very poorly controlled chronic hyperglycemia (the condition in which blood sugar level is too high) that lead to different challenges especially vascular, including the small vessels (microvascular) and large vessels (macrovascular) complications or sometimes both (Mbanya & Sobngwi, 2003). It usually affects the diabetic patients and may become serious if not treated. People with lower blood sugar levels may also have diabetes mellitus (hypoglycemia) (Cryer, 2012). Renal disease, cardiovascular disorders and cerebrovascular risk, inflammation, and obesity are serious complications, caused by DM (Shanker et al., 2011). Both types of DM are equally related to diabetes complications. Defective insulin production and disturbance in carbohydrate metabolism, protein, and lipids dysfunction lead to higher blood sugar levels which causes long-term complications (Kowluru & Chan, 2007). Diabetes causes boosted levels of endothelial microparticles (Mikirova et al., 2011). If the patient with hyperglycemia is remained unexamined for a long time it may cause diabetic ketoacidosis (DKA) in the patient. The symptoms of DKA include nausea, vomiting, and a higher level of ketones in blood and urine (Ali, 2011), additionally, Grave's disease, and Addison's disease anemia are autoimmune disorders that are analyzed in diabetic patients (Joffe et al., 2010). Hypertension, retinopathy, neuropathy, nephropathy, dyslipidemia, cardiomyopathy, atherosclerosis immune suppression, electrolyte imbalance, and pregnancy are the complications of DM that are grouped under microvascular, macrovascular, and miscellaneous complications (Sayin et al., 2015).

9.1. Microvascular complications

It covers 3 common and wreaking phenomena of diabetes mellitus:

- Retinopathy
- Nephropathy
- Neuropathy

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These complications are promoted by chronic hyperglycemia by the mechanism of induction of a proinflammatory microenvironment and, the creation of oxidative stress (Wild et al., 2004). Microvascular complications also reduce the skin healing process after injury, which may cause rooted ulcers that may be easily infected by microbes and parasites. So, a slight cut can cause serious issues, particularly at deeper levels, but the control of glucose level can delay the complications progress but may not resolve them.

9.1.1 Retinopathy

Diabetic retinopathy (DR) is a condition that is caused by chronic hyperglycemia and prolonged diabetes in which microvascular damage occurs to the retinal vessels, which also leads to edema and hemorrhage in the retina (Scott et al., 2007). In the body retina is the most vascular area, which needs a high oxygen level to convert light into electrical signals in the cones and rods of the eye (Yu & Cringle, 2001). It is mostly seen in both types of diabetes (Type I and Type II). It is the most common cause of adult blindness in the United States (Roy et al., 2004). Its early diagnosis is background retinopathy (non-proliferative diabetic retinopathy NPDR) and later diagnosis includes macular edema and proliferative retinopathy. Proliferative retinopathy is the most adverse form of the disease (Kollias & Ulbig, 2010).

Patients of DM also show dysglycemia earlier to diabetes symptoms and its diagnosis. In DR, vision loss over time, shadows in vision, trouble in vision hyperlipidemia are observed. Its prognosis is highly variable (Rema & Pradeepa, 2007). Ophthalmologists screen and diagnose the patient with DM regularly, to check the symptoms of retinopathy, and a fluoroscopy of the eyes is done. Its treatment is to control blood pressure and intensive glycemic but the treatment of early vision loss control is critical.

9.1.2 Nephropathy

Diabetic nephropathy is a kidney disorder in diabetic patients. With time nephrons (bottom of glomerular membrane) are thickened and glomerular sclerosis occurs with an abundance of excretion of extracellular matrix. This syndrome remains hidden until kidney damage or failure occurs. People with diabetic nephropathy may feel lower appetite, swelling in their legs, nausea,

vomiting, and restlessness (Smith & Singleton, 2012). It is observed in both cases (Type 1 and Type 2 DM). In the urine minimal amount of protein (microalbumin) is present but it remains unobserved in routine. It can be detected by sensitive tests and its progression can be prevented. Hypertension is the adverse cause of progressive renal failure (Veneti & Tziomalos, 2021).

9.1.3 Neuropathy

DM is a disease that is associated with chronic diseases of the central nervous system (CNS) and peripheral nervous system (PNS). Diabetic nephropathy is a microvascular complication of diabetes that causes dysfunction of nerves or neurons and impairment of intracellular metabolic activity due to chronic blood sugar levels. There are several types of diabetic neuropathy; including symmetrical form which is sensory (causes diabetic foot ulcer), autonomic radiculopathy (affects the proximal lumbar and causes weakness, pain, and abdominal pain), cranial (it affects the 3rd cranial nerve and causes diplopia) and asymmetrical which may be sensory or motor or both, affecting the peripheral and cranial nerves. It affects mainly older people. Vomiting, diarrhea, constipation, nausea, loss of function of hands, feet, and arms, indigestion, and problems with urination are the symptoms of neuropathy (Bansal et al., 2006).

9.2 Macrovascular complications

Enlarged vessel atherosclerosis is due to hyperinsulinemia, dyslipidemia, and hyperglycemia which are the indicators of DM. Myocardial necrosis, ischemic attack, peripheral arterial disease, and strokes are the symptoms of atherosclerosis.

9.2.1 Cardiovascular disease (cardiomyopathy)

Heart failure due to impaired function of systolic and diastolic blood pressure after myocardial infarction is known as cardiomyopathy. Hypertension, microvascular disease, endothelial dysfunction, obesity, and metabolic malfunction are the risk factors for cardiomyopathy (Sander & Giles, 2003). Type 2 Diabetes mellitus (T2DM) increases the risk of cardiovascular disease about 4 times in the whole population (Jude et al., 2010).

9.2.2 Cerebrovascular disease

Ischemic attacks and stroke are the most common causes of cerebrovascular diseases in diabetic patients. It affects the blood flow toward the brain and causes stroke, furthermore, after one stroke the chance of mortality and disability increases in diabetic patients. Hardening of vessels, high blood pressure, loss of balance, double vision, headache, and confusion are the symptoms of cerebrovascular disease (Nather & Tan, 2023).

9.3. Other complications of DM

9.3.1 Cancer

In the case of T2DM, kidney cancer, bladder cancer, breast cancer, and liver cancer may be elevated depending on the site of the cancer. T2DM and cancer have common risk factors such as aging, obesity, smoking, life habits, higher consumption of fats and carbohydrates, and psychological effects that cause carcinogenesis (Noto et al., 2010).

9.3.2 Infection

Hyperglycemia severely affects the function of granulocytes and T cells, in patients with uncontrolled diabetes who are at more risk of producing bacterial and fungal infections. People are more susceptible to oral and vaginal candidiasis disease, foot infection (osteoporosis and osteoarthritis). People with minor cuts are at more risk of developing infection (Casqueiro et al., 2012).

- Dermatological disorders affecting the skin (Mahajan et al., 2003).
- Depression.
- Hepatobiliary diseases (cirrhosis) (Farrell & Keeffe, 1998).

These are the common complications associated with DM.

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10. Genetics of Diabetes Mellitus

As we have already discussed, Type I Diabetes is caused by the degradation of beta cells. The genetic susceptibility of Type I Diabetes Mellitus is 35-55% and is associated with the with HLA class 2 genes (Noble et al., 2010). Other than that, non-HLA genes that causes less risk of Type I Diabetes are insulin gene on locus 11p15 and T-lymphocyte-linked protein CTLA-4 gene on the chromosome 2q33. The two loci of HLA genes that significantly increase the incidence of Diabetes are HLA-DRB1 and HLA-DQB1 (Desai et al., 2007). One of the alleles that cause diabetes in children is HLA-DR3 or DR4 (Deschamps et al., 1990). The genes causing the diabetes depend on the family history and genetic mutations of chromosomes. Besides that, some haplocytes such as HLA-DQA1*0102 and HLA-DQB1*0602 are protective against Type I Diabetes Mellitus (Redondo et al., 2006). The genetic map of Type II Diabetes Mellitus describes that the occurrence of the disease is 45% if one of the two parents is ill and 70% if both parents have diabetes. Studies revealed that two genes, CAPN10 and TCF7L2 are greatly responsible for T2 diabetes mellitus (Christodoulou et al., 2019). The former gene is located on the chromosome 10q and is common in Mexican Americans. It is a transcription factor that encourages insulin resistance and glucagon secretion from intestinal endocrine cells in Wnt signaling pathway (Yi et al., 2008). CAPN10 is a cysteine protease enzyme that assists in glucose digestion and catabolism (Ono et al., 2022).

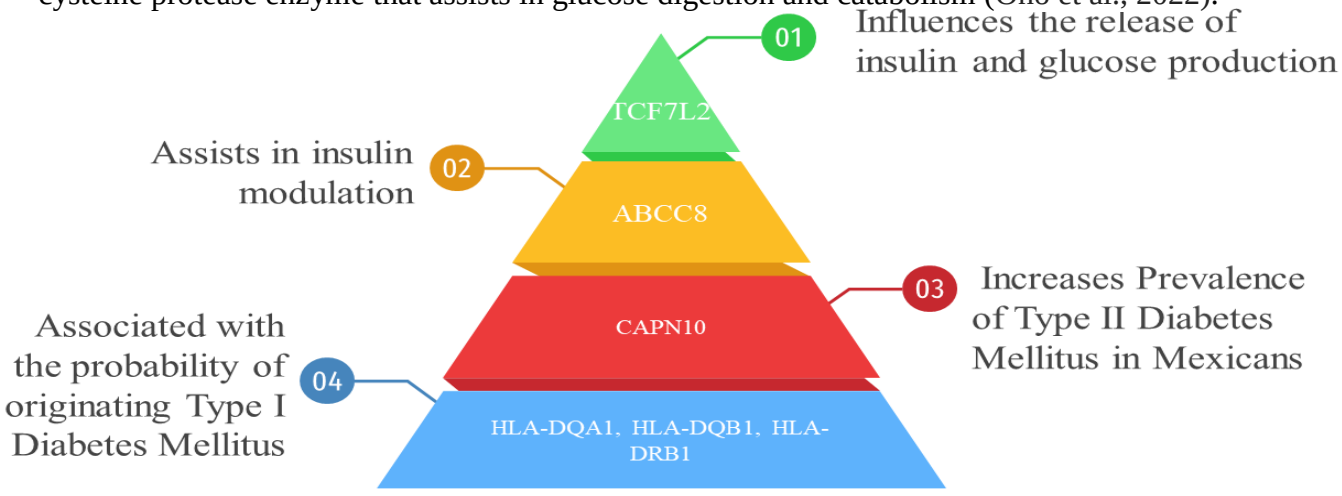

Fig 4: Genetic Factors Associated with Diabetes Mellitus

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11. Current Research and Future Directions

The research team of America estimates that the number of pre-diabetic patients will climb from 90.6 million in 2015 to 107.7 million in 2030 (Glurich & Acharya, 2019). Nowadays, only 10% of the adult population with pre-diabetes are aware of their condition, and without any intervention, they will develop diabetes in the next 5 years. There is a rapid spread of diabetes type 2 in developing countries and its prevalence depends on rural and urban areas. Future directions for diabetes depend on several factors that include proper primary prevention of diabetes, clinical measures and over-treatment measures, and ways to control diabetes in the pre-stage (Standl et al., 2019). Meanwhile, clinical endpoints and mortality rates are more important, future studies should add functional outcomes that are interesting for particular adults. The incorporation of proteomics, metabolomics, and transcriptomic data can provide more insights into the subcellular pathways and their relationships (Zhu et al., 2019). Research on these areas has already brought new changes and advancements in systemic metabolic processes. Transcriptomic studies of kidney tissues help clear molecular pathways that occur due to diabetes with specific cell types (Wilson et al., 2019). New and novel technologies are making it easier to understand molecular and structural phenotypes, thus making it easier to deal with the disease.

12. Conclusion

Diabetes is a significant worldwide disease and its prevalence is increasing day by day. Countries can take action with the objectives provided by WHO Global Action Plan, to minimize the impact of diabetes. Several programs and policies are required to ensure the technologies for proper management and diagnosis facilities. The importance of early detection and intervention to delay the onset of complications associated with the disease such as cardiovascular problems, neuropathy, retinopathy, and nephropathy. Management approaches including lifestyle modifications, insulin therapy, etc. can reduce the risk of diabetes. There is a need for comprehensive strategies at both individual and societal levels to combat the growing disease and improve the quality of life for affected individuals.

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