

## Diabetes Mellitus as a Disease and its Current Scenario - A Review

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### ABSTRACT

Diabetes mellitus is a chronic heterogeneous common metabolic disorder and a group of insulin resistance syndrome characterized by elevated blood glucose levels or hyperglycemia with complex pathogenesis. Diabetes mellitus results from abnormalities in either insulin secretion or insulin action or both. In current scenario Diabetes Mellitus is detected all over the world and a leading cause of death worldwide. This review includes different sections including classification, Clinical manifestation and complications, etiology, pathogenesis, diagnosis, treatment, and its relation with COVID-19. The common signs & symptoms observed in Diabetes Mellitus are Fatigue Polyphagia, Polydipsia, polyuria, vomiting, and dehydration. This disorder is mainly caused by the destruction of pancreatic beta cells and because of that it becomes autoimmune disorders. Some genetic factors, prior family history, environmental factors, autoimmune destruction and high insulin resistance increase the risk of the development of diabetes mellitus. In COVID-19-infected patients the Diabetes mellitus increases the significant complications and mortality rate.

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### Introduction

Diabetes Mellitus (DM) is a common endocrine metabolic disorder and one among the leading causes of deaths worldwide. It comprises of two words, the word “Diabetes” & “Mellitus” which are from the Greek language and the word “Diabetes” means “passer-by: a siphon” & word “mellitus” means “sweet” [1]. Diabetes Mellitus (DM), also known as complex metabolic disorder/insulin resistance syndrome characterized by hyperglycemia, a physiologically abnormal condition represented by continued elevated blood glucose levels [2]. It is a non-communicable disease in which hyperglycemia results from anomalies in either insulin secretion or insulin action or both and manifests in a chronic and heterogeneous manner as carbohydrate, fat, and protein metabolic dysfunctions. Diabetes follows a progressive pattern with complex pathogenesis and varied presentation [3]. Serious long-run complications of hyperglycemia are associated with, long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [4].

As per world Health Organization (WHO) criteria of 2024 about 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. Average medical expenditures among people with DM are about two times higher also Diabetes mellitus increase the risk of early death up to double, the scientific trends suggest that rates will constantly or frequently to increases. T1DM results in pancreatic cells being unable to produce enough Insulin. T2DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. GDM occurs when pregnant

women without previous diabetes mellitus develop high blood sugar levels. T1DM can manage by insulin injections. Treating T2DM involves maintaining a healthy diet, maintaining weight and physical exercise [5-7]. Diabetic patients are more rapidly or constantly rising throughout the World, which poses a great challenge to the Scientists and Clinicians currently [8].

### Types of Diabetes Mellitus

Diabetes is classified into four types as Type 1 Diabetes Mellitus (T1DM), Type 1 Diabetes Mellitus (T2DM), Gestational Diabetes Mellitus (GDM) & other specific types. Type 2 diabetes is the most common diabetes globally and it predominantly affects adults above thirty years of age although many cases have recently been diagnosed amongst obese children.

### Type 1 Diabetes Mellitus (T1DM) or Insulin Dependent Diabetes Mellitus (T1IDDM)

This type of diabetes mellitus is also known as Autoimmune Diabetes or Juvenile onset diabetes or ketosis prone polygenic disease [9,10]. This type of diabetes occurs mainly in children and adults; it develops before the age of 40. This type of disease occurs suddenly in teenagers were it may be life-threatening. T1DM can be handled or treated with Insulin, but there is no perfect cure. This form was previously known as “Insulin-Dependent Diabetes Mellitus” [9]. T1DM results from the pancreas’s failure to produce an adequate amount of Insulin due to loss of beta-cells, destruction of Beta-cells [11]. A large amount of sugar in the blood can lead to short-term and long-term problems. T1DM is a chronic metabolic syndrome defined by the inability of insulin production. The exact causes of T1DM are unknown [6]. Glucose from the food can’t enter cells resulting in increased concentration in the blood

stream, till date about 10% of people suffer from type 1 DM in the Worlds [12].

**Type 1 Diabetes Mellitus (T2DM) or Non-Insulin Dependent Diabetes Mellitus (T2NIDDM)**

T2NIDDM is also known as adult-onset Diabetes Insulin secretion defects identified in T2DM contribute to Insulin Resistance (IR). This form was previously known as "non-insulin-dependent diabetes mellitus" [9, 10]. It causes by insulin resistance and defects in beta cells due to glucose built in the bloodstream [13]. It is a progressive disease that develops in stages. A condition in which cells fail to respond to Insulin properly or reduced insulin level develops hyperglycemia and FFA [3].

**Gestational Diabetes Mellitus (GDM)**

It occurs in about 4% of all pregnancies and it has two classes - Class A1 & Class A2 [14]. It is the most common type of heritable kind of Monogenic disease women's who have suffered from ClassA2 need Insulin or other Medications. Gestational diabetes is the 3rd main type, and it occurs in pregnant women without a previous history of diabetes mellitus. GDM usually is detected in the later stages of pregnancy and often occurs in women who have no previous history of diabetes mellitus [9]. A fetus born with diabetes mellitus is the high risk of obesity & T2DM in future. ClassA1 are handled by Diet and Exercise. Gestational diabetes is projected to increase by approximately 18% globally [15].

**Other Specific Type of Diabetes Mellitus (Monogenic Types)**

This type of diabetes is of genetic abnormalities in the internal secretion of insulin hormone.1% to 5% of people may develop it from mutations. This includes diseases of the pancreas, certain Surgeries, Genetic defects in beta cells, Cancer Therapies,

medications & Infections etc. Some medicines are utilized or mixed with the treatment of HIV /AIDS or organ transplantation [16]. It's had sub-types MOODY, LADA & Endocrinopathies.

**Maturity Onset Diabetes of Young (MODY)**

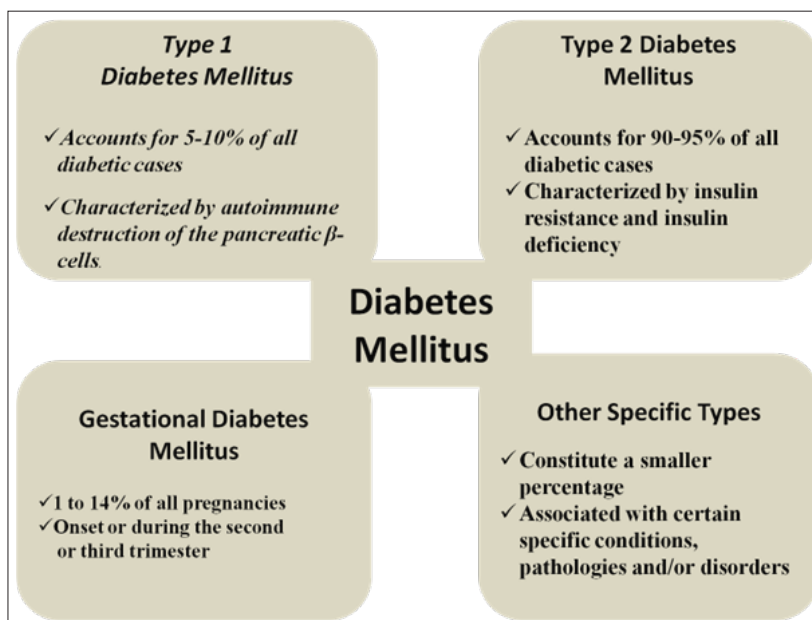
They may or may not be required Insulin. MODY stands for maturity onset diabetes of young [9]. MODY is inherited diabetes mellitus by a genetic mutation in an autosomal dominant gene that affects the secretion of insulin secretion or production & it's not insulin dependent diabetes. Individual diagnosis is generally in children less than age 25 with genetic factors. HNF1-Alpha (Hepatocyte Nuclear Factor) gene causes about 70% of cases of MODY [17]. It associates with a genetic defect of the beta cells. In this type occurs hyperglycemia at an early age. They are clinically closer to T2DM.

**Latent Autoimmune Diabetes in Adults (LADA)**

LADA stands for latent autoimmune diabetes in adults. After Diagnosis of this type of diabetes there is no need of Insulin for months to a year. They do not produce any insulin and it's clinically similar to T1DM, LADA occurs because pancreatic cells stop insulin production. LADA is present in young adults in their twenties & can be confused with type 2 diabetes mellitus because of age [18].

**Endocrinopathies**

Several hormones play activity on insulin action or inhibit insulin action. Impaired fasting blood glucose presents as an FBG higher than 100mg/dl but less than 126 mg/dl [18]. It may include polycystic ovarian syndrome, pancreatic cancer or tumors & other hormonal Disruptions in insulin production.



**Difference Parameters of Diabetes Mellitus**

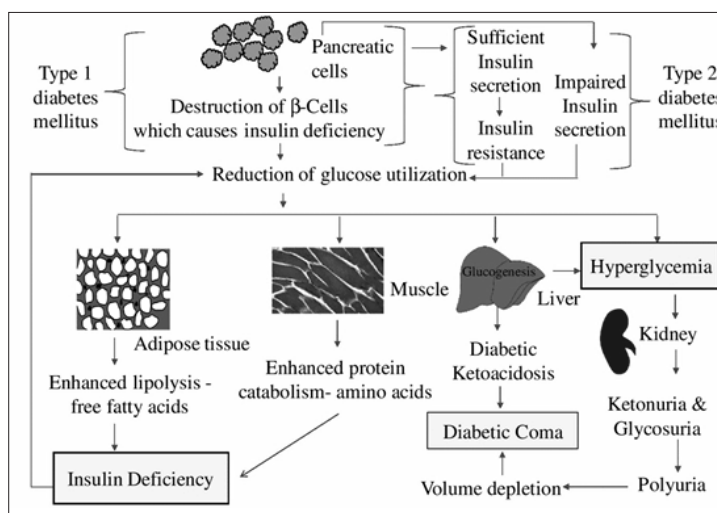
	T1DM	T2DM	MODY	LADA
Typical Age of Onset	Youth	Adult	Youth	Adult
Presence of Autoantibodies	Yes	No	No	Yes
Insulin Dependence	Yes	No	Not Always	Yes, within years
Insulin Resistance	No	Yes	Yes	No
Progression to Insulin Dependence	Rapid	Slow	Slow	Month/Year

### Etiology of Diabetes Mellitus

Sometimes chemicals & drugs are causes of T1DM other causes are autoimmune disorders (Graves’ Disease, Hashimoto’s Thyroiditis & Addison’s disease) and is serious causes of this type of diabetes mellitus [9]. In about 70 – 80% of cases, beta-cells are destroyed the immune system. In T1DM, the beta cells fail to produce Insulin. T1DM is commonly caused by the destruction of beta-cells. The cause of this autoimmune response is unknown T1DM characterized by Anti-Glutamic acid decarboxylase, due to the improper use of insulin, the glucose level decreased in the body, the leading cause of Type2DM. It’s also caused by Overeating, smoking, alcoholism, dysfunction of the endocrine & nervous system [19 - 21]. In T2DM, the body fails to utilize Insulin. Some traditional groups have a higher inherited incidence of it. The body produces a hormone called Insulin that maintains normal blood sugar levels. During pregnancy, the placenta produces higher pregnancy hormones that can interfere with Insulin. The body can make more insulin during pregnancy to keep blood glucose levels normal. Still, in some women, the body cannot make sufficient insulin during pregnancy and blood sugar levels grow up & it’s causing GDM. The main cause of diabetes Retinopathy is blindness & it causes 2.6% of global blindness [22].

### Pathophysiology of DM

The Pathophysiology of Diabetes mellitus is shown in below figure [23].



### Clinical Manifestation and Complications

Clinical manifestation in diabetes patients is similar in both type 1 and type 2 diabetes but the intensity of the clinical features differs. Major symptoms include polydipsia (excessive and prolonged thirst), polyphagia (excessive hunger) and polyuria (excessive urination), weight loss, cramps in muscles of the limbs, blurred vision, constipation and fatigue. The progressive nature of diabetes over time is associated with two types of long-term diabetes complications: macrovascular and microvascular. The latter usually occur earlier and may involve retinopathy, nephropathy and peripheral neuropathy. The former may lead to coronary heart disease, stroke, peripheral vascular disease and damage or loss of vision, extremities and kidney [24].

### Diagnosis of Diabetes Mellitus

Diabetes is diagnosed by testing the blood glucose/ sugar levels. Blood is tested before eating some food. Mostly it performs in the morning time before breakfast (Table 3). If a blood sugar level after fasting blood sugar level will be increased above 125 mg/dL, hence diabetes mellitus is diagnosed.

Also blood pressure, weight & feet are examined. Obesity greatly raises a person’s risk for T2DM. High BP often present in people with T2DM, which together with diabetes, will increase the risk of cardiovascular diseases. A weak pulse in the feet is condition that can prevent or reduce foot sore healing & possibly amputation. To decrease the risk of ulceration or re-ulceration by using specialized footwear’s [7].

#### Laboratory Tests

Test	Normal ( mg/dL )	Pre-Diabetes (mg/dL)	Diabetes (mg/dL )	Ref
Fasting Plasma Glucose Test Oral Glucose Tolerance Test	<100 mg/dL <140 mg/dL	100 – 125 mg/dL 140 – 199 mg/dL	>126 mg/dL >200 mg/dL	[23]
Random Blood Glucose Test	NA	NA	>200	
Hemoglobin A1C Test	<5.7 %	5.7 – 6.4 %	>6.5 %	

### Diagnosis of GDM

O’Sullivan Test: This test is used to examine GDM. A fasting patient is given 50g of glucose. Blood is drawn at every hour. GDM is indicated by plasma levels above 1500mg/dL [18].

## Treatment of Diabetes Mellitus

T1DM is unavoidable because it's caused by a problem with the immune system. Most diabetes prevention or treatment strategies involve making simple changes to your diet and fitness routine. Some causes of T2DM, such as your genes or age, are out of your control. Yet many other diabetes mellitus risk factors are manageable. These aren't the only ways to prevent diabetes mellitus. Diabetes Mellitus is a chronic disease with an unknown cure [7].

### Some Things can Delay or Prevent T2DM

Get at least 20 min/day of aerobic exercises. In overweight condition try to lose 7% weight as a reliable source. The diet excludes refined carbohydrates from your diet. Eat many more fruits, vegetables and whole grains daily. It may be possible to manage by eating healthy foods, exercising, and maintaining healthy body weight. The goal of treatment is to maintain healthy blood glucose levels and to prevent diabetes mellitus related complications.

### Diet

A high fiber & low-fat diet based on fruits, vegetables, and whole grains are suggested by doctors. Avoid clarified sugar containing foods. Alcohol contains a lot of sugar, so consumption of alcohol (Alcoholism) should be reduced [25, 26].

### Exercise

Exercise effect on Physical, Mental & Social health. Exercise helps to lower blood glucose levels. Regular exercise also helps maintain healthy body weight and control high blood pressure and high blood cholesterol levels [27]. This, in turn, helps to reduce the risk of related health conditions such as cardiovascular diseases. Sitting still (i.e. being sedentary) for long periods is a risk factor for T2DM. You should aim to get up regularly and move around for a few minutes [26].

### Weight

Overweight is high risk. People with T2DM and overweight (BMI > 35) may be able for weight-loss surgery (bariatric surgery) [22, 26].

### Skin

DM causes some skin related complications such as Bacterial & Fungal Infections, Itching and some Allergic reactions etc., [28].

### Family History

The high risk of T2DM due to family history [22].

### Age

Risk of diabetes increases as you get younger, especially after 45 years old [22].

### Blood Glucose Monitoring

Depending on a person's treatment plan, their blood glucose levels may require be checking and noting from time to time or, if treated with Insulin, several times a day. Many factors can interfere with blood glucose levels, so careful measure is the way to ensure that blood sugar levels remain within their normal range [26].

Two blood glucose level problems requiring immediate attention are,

- **High blood glucose (hyperglycemia):** Eating too much food or not taking enough diabetes medication can result in a blood glucose level that is too high. Hyperglycemia is a life-

threatening condition that requires immediate hospitalization to prevent complications & death of the patient [29].

- **Low blood glucose (Hypoglycemia):** It defines a blood sugar level <70 mg/dL. Blood glucose levels can drop for many reasons, e.g., skipping, taking diabetes medication, or exercising more than usual. Hypoglycemia is most likely when taking insulin or diabetes medications that promote the secretion of Insulin. Drinking or eating something sweet will correct a low blood glucose level [26].

**Insulin Therapy:** People with T1DM need insulin therapy [30]. The goal of insulin therapy is to maintain or control blood sugar level. It's administrated subcutaneously using a syringe, insulin pen or insulin pump (Table 4). Insulin therapy is the most important part of T1DM & sometimes for T2DM [31].

### Islet Replacement Therapy

Insulin injections are traditional in vitro therapy that cannot correctly cure diabetes mellitus. Islet replacement therapy is an alternative treatment for diabetic patients. In this therapy, insulin producing beta-cells are replaced with pancreas or islet-cell transplants [32]. It's used sometimes because low success rate. Instead, this major transition from conventional/ traditional Insulin to islet transplants has some challenges such as limited donors, proper functioning of islet grafts, long term survival etc [33].

### Stem Cell Therapy

Stem cells are responsible for the development of the whole human body. Stem cell therapy is used to treat T1DM. To cure T1DM, replacing stem cells must be more than just a case of alternate Insulin generating cells from the pancreas those diminished by diabetes in diabetic patients [32]. This property of stem cell is help to the proper functioning of pancreatic beta cells that are production a sufficient amount of insulin to maintain blood glucose level (Table 5).

### Common Diabetes Medications for Diabetes Mellitus

If some lifestyle changes are inadequate or unable to control its blood glucose level, maybe need some medications are required.

### Diabetes Mellitus and COVID-19

Diabetes mellitus is a well-known risk factor for worse clinical outcomes in patients with Coronavirus Disease 2019 (COVID-19). However, the relationship between these two entities seems to be bidirectional [34]. The pandemic of COVID-19 has significantly affected blood glucose control in patients with diabetes. The results of these effects can be classified into direct effects (those directly related to the viral infection) and indirect effects (those related to the impact of the pandemic on the management of blood glucose or the use of proposed treatments for the infection that also affect glucose homeostasis). As a direct effect, the COVID-19 infection has resulted in striking changes in patients' metabolism with significant elevations in blood glucose. It is attributed to the increased release of cytokines and inflammatory mediators, which led to increased insulin resistance and the associated hyperglycemia [2].

### Type 2 Diabetes Mellitus as a Risk Factor for COVID-19

Type 2 Diabetes Mellitus (T2DM) is considered a risk factor for a poor prognosis in COVID-19 [1]. Many mechanisms have been described to explain the poorer prognosis of COVID-19 in diabetics. Some of these mechanisms include impaired neutrophil degranulation and complement activation, increased glucose

concentration in airway secretion, which significantly increases viral replication, exaggerated pro-inflammatory cytokine response in diabetes, decreased viral clearance, and more significant presence associated comorbidities [15]. One of the essential aspects of the relationship between COVID-19 and T2DM is that the information on the condition of hyperglycemia at the time of hospital admission is more relevant for prognostic purposes than the HbA1c. It is thought that COVID-19 predisposes infected individuals to hyperglycemia, leading to hyperglycosylation of the angiotensin-converting enzyme 2 (ACE2), the natural viral receptor on the host cell surface [16]. The acute hyperglycemia in these patients induces inflammation, endothelial dysfunction, and thrombosis via the generation of oxidative stress [2]. This may also enhance tissue tropism and viral penetration into the cells leading to increased virulence, pathogenicity, and susceptibility to severe infections. It has been hypothesized that the COVID-19 might affect pancreatic B-cells to produce insulin, which would aggravate underlying lack of glycemic control in the setting of T2DM [17]. Regardless of the mechanisms, when comparing COVID-19 patients with and without T2DM, the patients with T2DM tend to develop more severe forms of the disease and have a significant increase in inflammatory markers compared to non-diabetics (i.e., higher levels of C-reactive protein, procalcitonin, ferritin, lactate dehydrogenase, and d-dimer) [18]. Understanding the interactions between these two diseases is crucial in developing appropriate therapeutic approaches. Further studies are warranted to elucidate the mechanisms by which diabetes affects these patients' prognosis and how these pathways can be modified to generate better outcomes in COVID-19 patients with diabetes.

### COVID-19 and Type 1 Diabetes Mellitus

The prevalence of type 1 Diabetes Mellitus (T1DM) in COVID-19 patients ranges between 0.15% to 28.98% [21]. Hyperglycemia has been observed to be a risk factor for COVID-19-related complications. According to preliminary findings from a multicenter surveillance study in the United States that assessed clinical outcomes of COVID-19 in patients with T1DM, a total of 48.5% of patients had high blood glucose levels; 45.5%, elevated temperature; 39.4%, dry cough; 33.3%, excess fatigue, and vomiting; 30.3%, shortness of breath; 27.3%, nausea; and 21.2%, body/headaches [22]. Additionally, abdominal and chest pain, chills, loose stools, and loss of taste and smell were reported by <15% of patients [22]. In these patients with COVID-19 and T1DM, obesity (39.4%) and hypertension or cardiovascular disease (12.1%) were the most prevalent comorbidities, while diabetic ketoacidosis was the most common adverse outcome [22]. In a whole-population study that assessed the independent effects of diabetic status and its type on in-hospital death in English patients with COVID-19, 1.5% of in-hospital COVID-19-related deaths were occurred in patients with T1DM versus 31.4% in those with T2DM [23]. A population-based cohort study assessed the associations between risk factors and mortality due to COVID-19 in patients with T1DM [24]. Older age and male sex were found to be closely associated with increased COVID-19-related mortality [24]. Additionally, mortality was significantly higher among the socioeconomically deprived individuals and preceding HbA1c (HbA1c > 86 mmol/mol) was also strongly associated with COVID-19-related mortality [24]. Impaired renal function and previous hospital admissions with stroke or heart failure were closely associated with COVID-19-related mortality ( $p < 0.0001$ ) [24, 25]. Among newly diagnosed patients with diabetic ketoacidosis (DKA), the proportion of patients with severe DKA in 2020 was 44.3% compared to 36.1% in 2019, hence, the COVID-19 pandemic might have changed the presentation of diabetes and the severity of DKA [25].

### Conclusions

The above review has given information about Diabetes Mellitus, Types, Signs & Symptoms, Causes, Diagnosis, and Treatment. Diabetes Mellitus become a common disease among children and more severe if no initiative is taken to control it. Diabetes Mellitus is a Non-Curable (Incurable) Disease, but it can handle or Prevent by Insulin Therapy & Anti-Diabetic medicines for a while. Proper diet and exercise for diabetic's patients is a must. 80-90% of Diabetic Patients suffer from T2DM in India & US. If not appropriately treated, the disease will affect 90 – 95% of the World's population & it will generally appear in people of all age's in the future. Diabetes mellitus is associated with a significant risk of complications, extended hospital stays, and mortality in COVID-19 infected patients [26-43].

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