CHAPTER 1

INTRODUCTION

1.1 Diabetes Mellitus

Diabetes Mellitus (DM) is a chronic metabolic disorder clinically characterized by hyperglycemia. The myriad pathogenic mechanisms for diabetes mellitus arises from both genetic and environmental factors, which is due to insufficient insulin secretion, reduced responsiveness to endogenous or exogenous insulin, abnormal glucose production, or abnormalities in fat and protein metabolism. It affects all age group people in the different geographical region [1, 2].

1.2 Classification of DM

Based on pathogenesis, the age of onset, and type of therapy, there are broadly divided into

- **Type 1 or IDDM (Insulin Dependent Diabetes Mellitus)** - the pathogenesis of type 1 DM is an autoimmune disorder or idiopathic, develops in childhood (Juvenile diabetes) or early adulthood, and some latent forms. It requires insulin therapy. It accounts for 5-10% of diabetes.

- **Type 2 or NIDDM (Non-Insulin Dependent Diabetes Mellitus)** - mainly due to impairment in the metabolism of carbohydrates, proteins, and lipids. It affects 80% of individuals.

- **Gestational Diabetes Mellitus (GDM)** – it is due to impaired glucose intolerance, recognized during pregnancy. It complicates about 7% of all pregnancies. Early diagnosis and treatment prevent perinatal morbidity and mortality. These people have a substantial risk (30 to 60%) of developing DM later in life.

- **Other specific types of diabetes mellitus** - The major contributors to this type of diabetes are genetic defects, diseases of pancreas, endocrine glands, infections, drugs, and chemicals [1-3].
1.3 Epidemiology

The incidence of diabetes mellitus is alarmingly raising for the past two decades. The prevalence of both type 1, and type 2 diabetes mellitus is increasing worldwide but the prevalence of type 2 DM is expected to rise more rapidly in the future. The factors that contribute to the rise in type 2 diabetes are obesity in childhood and adolescence, reduced physical activity levels, and poor nutrition in individuals [4, 5].

As per International Diabetes Federation (IDF) 2017, worldwide 473 million people will have type 2 DM by the year 2045. Moreover, studies were shown that the people in urban areas are more prone to diabetes than rural people. In India, 72.9 million people are suffering from diabetes, and several people were with undiagnosed diabetes. It is expected to raise 134.3 million in 2045 and will cross China and occupy 1st place in the world [6, 7].

![Figure 1.1: International Diabetes Federation Survey on Type 2 DM [6]](image)

1.4 Signs and Symptoms

The common signs and symptoms of DM are polyuria, polyphagia, polydipsia, nocturia, tiredness, fatigue, lethargy, change in weight, blurred vision, pruritus vulvae, balanitis (genital candidiasis), nausea, headache, hyperphagia, the predilection for sweet
foods, mood change, irritability, difficulty in concentrating, apathy, numbness or tingling in the hands or feet and delayed wound healing [3,8, 9.]

1.5 Diagnosis

The World Health Organization and National Diabetes Data Group have issued diagnostic criteria for DM which has been tabulated below.

**Table 1.1: Diagnosis of Type 2 Diabetes Mellitus**

<table>
<thead>
<tr>
<th></th>
<th>Normal Glucose Concentration</th>
<th>Impaired Glucose Concentration</th>
<th>Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random blood glucose concentration along with symptoms of diabetes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>≥ 200 mg/dL (11.1 mmol/L)</td>
</tr>
<tr>
<td>Fasting plasma glucose mg/dL (mmol/L)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt; 100 (5.6)</td>
<td>100–125 (5.6–6.9)</td>
<td>≥ 126 (7.0)</td>
</tr>
<tr>
<td>In OGTT, two hours after glucose load mg/dL (mmol/L)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt; 140 (7.8)</td>
<td>≥ 140–199 (7.8–11.0)</td>
<td>≥ 200 (11.1)</td>
</tr>
<tr>
<td>Glycated hemoglobin (HbA&lt;sub&gt;1c&lt;/sub&gt;) (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt; 5.7</td>
<td>5.7–6.4</td>
<td>≥ 6.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Random is defined as without regard to time since the last meal.

<sup>b</sup> Fasting is defined as no caloric intake for at least 8 h.

<sup>c</sup> A glucose load containing the equivalent of 75 g was dissolved in 300 mL of water and given to an overnight fast in persons, not recommended for routine clinical use.

<sup>d</sup> HbA<sub>1c</sub> of ≥ 6.5% is considered as diabetes that reflects the state of glycemia over a period of 8-12 weeks. The diagnostic test should be done in patients with plasma glucose levels ≥ 200 g/dL (11.1 mmol/L) [2,3,9].

1.6 Risk Factors

DM is a multifactorial disease with a wide range of risk factors and their complex interplay making it tough to manage or prevent. Recently, it has been reported that Vitamin D also plays a significant role in glucose intolerance and insulin
secretion. Similarly, Vitamin K increases the insulin sensitivity and glycemic status of the patient. Deficiency of Vitamin D and K also increases the susceptibility for type 2 diabetes mellitus [13]. Other well validated risk factors known from years were listed below.

- Family history of diabetes
- Obesity (BMI ≥ 25 kg/m²)
- Habitual physical inactivity
- Race/ethnicity
- Previously identified impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
- History of GDM or delivery of baby > 4 kg (> 9 lb)
- Hypertension (blood pressure ≥140/90 mmHg)
- Dyslipidemia (HDL cholesterol level ≤ 35 mg/dL (0.90 mmol/L) and/or a triglyceride level ≥250 mg/dL (2.82 mmol/L)
- Polycystic ovary syndrome or acanthosis nigracans
- History of vascular disease [10 -13].

1.7 Pathogenesis of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is a heterogeneous syndrome, characterized by three pathophysiologic abnormalities that are impaired insulin secretion, peripheral insulin resistance, and excessive hepatic glucose production. Development of type 2 DM predominately depends on genetics. The risk of development of type 2 DM in offspring is at least 15% [14, 15].

1.7.1 Impaired Insulin Secretion

The sensitivity of pancreatic β cell is altered in type 2 diabetic patients. Impaired responsiveness of the pancreatic β cell to stimuli like neural signaling, glucose-dependent insulin-releasing peptide (GIP), and insulinoergic gastrointestinal hormones (glucagon-like peptide-1 (GLP-1) results in the inadequate and delayed production of insulin release that triggers glucose production from the liver, and hormones in different pathways resulting in hyperglycemia. Higher levels of fasting blood glucose stimulate increased insulin production in these patients that leads to the development of insulin resistance.
Chronic hyperglycemia, insulin resistance, and deposition of amylin or islet amyloid polypeptide (IAPP), co-secreted with insulin, paradoxically impairs pancreatic islet function and reduces β cell mass [14 - 16].

1.7.2 Insulin Resistance

Insulin sensitivity is normally measured to know the amount of glucose cleared in the blood in response to administration of a fixed dose of insulin. Impaired insulin secretion fails to clear the blood glucose levels, this condition is referred to as insulin resistance. The loss of sensitivity of insulin receptors, defects in insulin signaling mechanism, and several other factors contribute to insulin resistance (IR), but the primary cause is unclear [9, 14].

The most common factor for IR was obesity, adipocytes, and immune cells. They produce adipocytokines, IL-6, resistin, TNF-α, and retinol-binding protein 4, that compete with glucose uptake by skeletal muscles, liver, and adipose tissue resulting in systemic IR. The second major determinant of IR was physical inactivity. Physical inactivity is associated with downregulation of insulin-sensitive kinases that promotes accumulation of free fatty acids within skeletal muscle and reduce the uptake of glucose. Recent studies revealed that the molecular pathogenesis of IR is due to the defect in phosphatidylinositol 3-kinase signaling pathway which reduces translocation of GLUT4 to the plasma membrane. Insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output, both effects contribute to the hyperglycemia [3, 14, 15].

1.7.3 Increased Hepatic Glucose Production

Insufficient insulin secretion and excess glucagon production in response to insulin resistance in type 2 DM stimulate the hepatic cells that leads to hyperglycemia. Moreover, it causes deposition of fat in the liver leading to non-alcoholic fatty liver disease (NAFLD) in response to hepatic insulin resistance. This is associated with central obesity in type 2 diabetic patients [14, 16]. Excess accumulation of lipids desensitize the insulin receptors in adipose tissue and muscle leading to lipolysis. Increased lipolysis contributes to activation of de novo gluconeogenesis resulting in increased hepatic
glucose output. Several studies have shown that increased glucagon levels in diabetic patients stimulates liver, resulting in abnormal glucose production [17].

**Figure No. 1.2: Pathogenesis of Type 2 Diabetes Mellitus [14]**

### 1.8 Complications of Type 2 DM

Type 2 DM people are more vulnerable to both short and long-term complications of diabetes. There are broadly divided into two major categories, acute and chronic complications.

**Figure No.1.3: Complications of Type 2 DM [18]**
1.8.1 Acute Complications of diabetes mellitus

Acute complications of diabetes mellitus are diabetic ketoacidosis, hyperglycemic hyperosmolar non-ketotic syndrome, and hypoglycemia [18].

1.8.1.1 Diabetic Ketoacidosis

Mostly observed in type 1 diabetes mellitus patients, also occurs in patients with type 2 DM. The complications of DKA are developed over a period of 24 hours. They show characteristic symptoms and physical inactivity [19].

1.8.1.2 Pathogenesis of DKA

Relative and absolute deficiency of insulin, along with the excess production of glucagon, cortisol, growth hormones, and catecholamines in diabetic patients results in gluconeogenesis, glycogenolysis, and ketone body formation from the liver [11]. Increased free fatty acid production results in ketosis, a condition that alters the pH of the blood too acidic (pH < 7.3)/ bicarbonate (<15mEq/l), hyperglycemia (>250 mg/dl) and Ketonuria [19, 20].

1.8.1.3 Clinical Manifestations of DKA

- Symptoms include nausea, vomiting, polyuria, thirst, abdominal pain, shortness of breath.
- Signs include tachycardia, dehydration/hypotension, dry mucous membranes/reduced skin turgor, tachypnea/respiratory distress/kussmaul respirations, abdominal tenderness (acute pancreatitis), lethargy/cerebral edema/ obtundation/coma.
- Precipitating events are inadequate insulin administration, infection (pneumonia, sepsis, gastroenteritis, urinary tract infections), infarction (cerebral/periphery, coronary, and mesentric drugs (cocaine), pregnancy [11].

1.8.1.4 Treatment of DKA

Continuous monitoring of blood glucose, maintaining insulin therapy, and correcting serum electrolyte imbalance, and avoiding dehydration were the main strategy in the management of DKA [9, 11].
1.8.1.5 Hyperglycemic Hyperosmolar State

It was primarily seen in patients with type 2 DM, occurs due to insulin deficiency, and inadequate fluid intake. Symptoms are similar to DKA, the physical examination reflects profound dehydration and hyperosmolality, and reveals hypotension, tachycardia, and altered mental status [20, 21].

1.8.1.6 Pathogenesis

The major contribution for HHS was hyperglycemia (>700mg/dl) due to gluconeogenesis, and glycogenolysis results in increased bicarbonate levels (>15mEq/l), (pH >7.3) and osmolarity (>320mosmol/l) that leads to osmotic diuresis, intravascular volume depletion, which is exacerbated by inadequate fluid replacement [21].

1.8.1.7 Treatment of HHS

Fluid replacement with normal saline, correcting serum electrolytes, insulin therapy were major approaches for management of HHS [14, 21].

1.8.2 Chronic Complications

![Complications of Diabetes Mellitus](image)

Figure No.1.4: Chronic Complications of Diabetes Mellitus [11]

Note: TIA: Transient ischemic attack; CVA: Cerebrovascular accident; ACS: Acute coronary syndrome; CHF: Congestive heart failure; PVD: Peripheral vascular disease.
Microvascular complications of type 2 diabetes include diabetic neuropathy, nephropathy and retinopathy [22]. Macrovascular complications are mainly associated with cardiovascular disorders like acute coronary syndrome, congestive heart failure, and peripheral vascular disease. In brain it induces transient ischemic attacks, and accumulation of advanced glycation products [23, 24].

Several studies indicate that the pathogenesis of DM are majorly due to genetics, lifestyle changes, epigenetic modifications and nutritional deficiency [25, 26].

1.8.2.1 Treatment of Chronic Complications

Chronic complications are prevented by diet management, regular exercise, other nutrients supplementation along with oral hypoglycemic agents [11, 14].

1.8.3 Insulin, its Role in CNS and Cognitive Impairment

In the brain, insulin exhibits multiple neurophysiological functions like survival of neurons, synapse, and dendrite plasticity. Experimental studies in animals have reported that the insulin receptors are abundantly found in areas closely related to cognition like cerebral cortex, hippocampus, hypothalamus, and olfactory bulb, and plays an important role in learning and memory process. It also regulates satiety, appetite, and behavioral function. Recent studies have shown that the uptake of insulin by the brain is mainly mediated through insulin receptors rather than CSF via Glucose transporter 4 (GLUT4) present in cerebellum and mainly in the hippocampus [27].

Studies have shown that insulin exhibits neuroprotective effect in brain by inhibiting apoptosis, ischemia, oxidative stress and beta amyloid induced cell death [28, 29]. Insulin is also well recognized for its neuromodulator effect in the central nervous system. It regulates the release of neurotransmitters in brain and their receptor density. Memory process is based on the neuronal network by long term potentiation and long term depression. Insulin modulates the glutamatergic transmission at the synapses and phosphorylates AMPA receptor at Serine 831 that is associated with maintenance of long-term potentiation in memory and learning process [30].
1.8.3.1 Effect of Insulin Resistance in Brain

Insulin resistance in brain results in

- Orexigenic peptide release and increases food intake,
- Decreased gonadotropin release resulting in hypothalamic hypogonadism,
- Decreased brown fat activity leads to hypothermia,
- Increased hepatic glucose output,
- Impaired response to hypoglycemia, and
- Impaired neural function (memory & mood) [31].

1.8.4 Type 2 DM and its Association with Cognitive Decline

Recent studies have suggested that diabetic people have increased risk of cognitive decline and it is considered as one of the complications of diabetes. Poor
glycemic control is the determining factor for cognitive dysfunction in patients with type 2 DM. Some studies have shown that diabetic patients are associated with decreased verbal memory, psychomotor speed, visual attention, work memory, complex motor functioning, recall (immediate & delayed), verbal fluency, and executive function [32-37].

The pathophysiology of this is not clear but several studies addressed that hyperglycemia and insulin resistance that is observed in impaired glucose tolerance are the major risk factors for cognitive impairment in diabetic patients. Hyperinsulinemia causes downregulation of insulin-degrading enzyme (IDE) levels in the brain, which is responsible for the degradation of insulin and amyloid β peptide (Aβ) in the brain that leads to accumulation of Aβ peptide and cognitive decline [30,38,39].

![Figure No.1.6: Type 2 Diabetes Mellitus & its Association with Cognitive Impairment](image)
Early diagnosis of cognitive impairment in diabetes mellitus is screened with help of biomarkers, neuroimaging, and genetic factors. This helps in preventing complications associated with diabetes [10, 40].

**Figure No.1.7: Biomarkers for Diabetes Associated Cognitive Decline [40]**

**Note:** 2h-PG: 2h-post prandial glucose; GA/HbA1C: glycated albumin/ Haemoglobin A1c; AGE: advanced glycation end products; sRAGE: Soluble receptor for advanced glycation end products; HOMA-IR: Homeostatic model assessment- Insulin resistance;
1.8.5 Pharmacology and Management of Diabetes Mellitus

Management of DM is a combined approach of multiple strategies to achieve a strict control of blood glucose levels. Among them pharmacotherapy constitutes a major area [14, 41]. The list of the drugs used in the management of DM and their adverse effects have been tabulated in the Table No.1.2.

![Figure No.1.8: Management of Diabetes Mellitus [41]](image-url)
Table No.1.2: List of Drugs for Treatment of Type 2 DM [14, 41]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Class</th>
<th>Drug(s)</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Insulin secretagogue-sulfonylureas</td>
<td>Second generation: glyburide, glibenclamide, glipizide, and others</td>
<td>Hypoglycemia, weight gain.</td>
</tr>
<tr>
<td>2.</td>
<td>Non-sulfonylureas</td>
<td>Repaglinide, nateglinide</td>
<td>Hypoglycemia,</td>
</tr>
<tr>
<td>3.</td>
<td>Biguanides</td>
<td>Metformin</td>
<td>Diarrhea, nausea, lactic acidosis.</td>
</tr>
<tr>
<td>4.</td>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose, miglitol, voglibose.</td>
<td>Gastro Intestinal flatulence, nausea, bloating, anorexia, abdominal discomfort, diarrhea and elevated liver function enzymes.</td>
</tr>
<tr>
<td>5.</td>
<td>Thiazolidinediones</td>
<td>Rosiglitazone, pioglitazone</td>
<td>Peripheral edema, CHF, weight gain, fractures, macular edema</td>
</tr>
<tr>
<td>6.</td>
<td>Dipeptidyl peptidase 4 inhibitors</td>
<td>Sitagliptin, saxagliptin, linaglaptin, alogliptin, vildagliptin</td>
<td>Increases risk of heart failure and hepatic failure.</td>
</tr>
<tr>
<td>7.</td>
<td>SLGT2 inhibitors</td>
<td>Canagliflozin, dapagliflozin, empagliflozin</td>
<td>Urinary tract and genital mycotic infections, hypotension, and DKA.</td>
</tr>
<tr>
<td>8.</td>
<td>GLP-1 agonists</td>
<td>Albiglutide, dulaglutide, exenatide, liraglutide</td>
<td>Hypoglycaemia, Nausea, weight loss.</td>
</tr>
</tbody>
</table>
1.8.6 Conventional Medicines and their Drawbacks

Type 2 diabetic patients are commonly treated with drugs like insulin secretagogues (Sulfonylureas), insulin sensitzers (Biguanides, Thiazolidinediones), alpha-glucosidase inhibitors, incretin-based therapies (Exenatide, Sitagliptin), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors table 1.2 [41].

Though conventional medications are effective, on long-term use it produces several side effects. Metformin is the most commonly used drug for type 2 diabetic patients vowing to its reduced risk of cardiovascular events and cost effectiveness. But it causes GI symptoms like nausea, bloating, anorexia, abdominal discomfort, and diarrhoea. Long term use of metformin results in vitamin B\textsubscript{12} deficiency not suitable for the patients with anaemia and peripheral neuropathy [42].

Sulfonylureas lowers both fasting and postprandial glucose levels. The major side effect associated with it was hypoglycemia and weight gain and it should use cautiously in patients with liver and renal dysfunction [43].

The major side effects of thiazolidinediones are fluid retention resembling peripheral edema, weight gain, and deposition of fat in subcutaneous tissue. It increases the risk of angina pectoris, myocardial infarction, fracture in women, and urinary bladder cancer [9].

Acarbose produces similar side effects like metformin. Gliptins cause hepatic failure and increase the risk of heart failure. Newer drugs like sodium glucose co-transporter 2 inhibitors also have reported frequent urinary tract infections. Patients not responding to oral hypoglycemic agents, need a combination of drugs and in later stages require insulin therapy [9]. Moreover the drugs are not effective in controlling the complications associated with type 2 diabetes mellitus.

Hence, there is need to develop a therapy that has fewer side effects than conventional drugs and more effective in the management of hyperglycemia and its associated complications in diabetes mellitus.