DIABETES MELLITUS

ABSTRACT

Diabetes is a chronic metabolic disorder characterized by high blood glucose levels due to insufficient insulin production, impaired insulin function, or both. It is a major global health issue, affecting millions worldwide and contributing to severe complications such as cardiovascular diseases, kidney failure, nerve damage, and vision impairment. With rising prevalence, diabetes prevention through diet, exercise, and early detection remains crucial in reducing its global burden. Addressing diabetes requires a multi-faceted approach involving public health policies, education, and advancements in medical research to improve patient outcomes and quality of life. This chapter explores the types of diabetes, their causes, symptoms, pathophysiology, risk factors, Lab diagnostics, and treatment.

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I. INTRODUCTION

Diabetes mellitus (DM) is a widespread chronic metabolic disorder characterized by elevated blood glucose levels, which result from either insulin resistance or a reduced ability to produce insulin. The term "diabetes" originates from the Greek word meaning "to pass through," while "mellitus" comes from the Latin word for "sweet." Diabetes is the sixth leading cause of death worldwide. The condition primarily affects the the cardiovascular system, as high blood glucose levels and insufficient insulin hinder glucose uptake by the body's cells. Individuals with diabetes may experience acute, life-threatening episodes such as ketoacidosis or hyperosmolar coma. As the disease progresses, complications like atherosclerosis, diabetic retinopathy, diabetic nephropathy, and nerve damage become more likely. Additionally, diabetes is a leading cause of dysfunction and failure in internal organs such as the liver, kidneys, and heart.[1,2]

II. EPIDEMIOLOGY

The global burden of diabetes is increasing at an alarming rate across the world. Countries with the highest prevalence include India, China, the USA, Japan, Russia, and Brazil. According to the International Diabetes Federation (IDF), approximately 537 million people are living with diabetes, which constitutes 10.5% of the global population. In 2021, an estimated 6.7 million people died due to diabetes-related complications.[3] The prevalence of diabetes is projected to continue rising, with estimates suggesting that the number of people living with diabetes will reach 643 million (11.3% of the global population) by 2030 and 783 million (12.2%) by 2045.[4]

III. BLOOD GLUCOSE

Glucose is the principal metabolic substrate for cellular energy production. During the gestational period, the developing fetus receives glucose from the mother. Fetal glucose levels typically fluctuate around 3 mmol/L. In the first few hours after delivery, the blood glucose level varies between 1.4 and 6.2 mmol/L. After 72 hour of life, Blood glucose values return to normal (3.5–5.5 mmol/L) for infants, children, and adults. Glucose contributes to nearly 80% of the fetus’s total energy requirements. The remaining 20 % is fulfilled by lactate, amino acids & glycerol. Fetus utilities glucose at higher rate than adults. Under normal circumstances, there is no fetal glucose production from gluconeogenic & glycogen lytic pathways. But it can be stimulated when fetus is subjected to prolonged periods of low glucose supply (eg, during placental insufficiency &

prolong fasting). Fetal liver possesses glycogenic enzymes from 8 weeks of gestation. [5] Human has complex hormonal mechanism to ensure it in normal levels. These hormones include Glucagon, Insulin, Epinephrine, Norepinephrine, Thyroxin etc.

Normal Blood Glucose Values in Adult

- Blood glucose fasting (Before meal): 70 to 110 mg/100 ml (3.89 to 6.11 mmol/liter)
- Blood glucose postprandial (2 hours):70 to 140 mg/100 ml (3.89 to 7.77 mmol/liter)
- Blood glucose random: 70 to 160 mg/100 ml (3.89 to 8.88 mmol/liter)

Hyperglycemia: High blood glucose level

Hypoglycemia: Low blood glucose level [7,6]

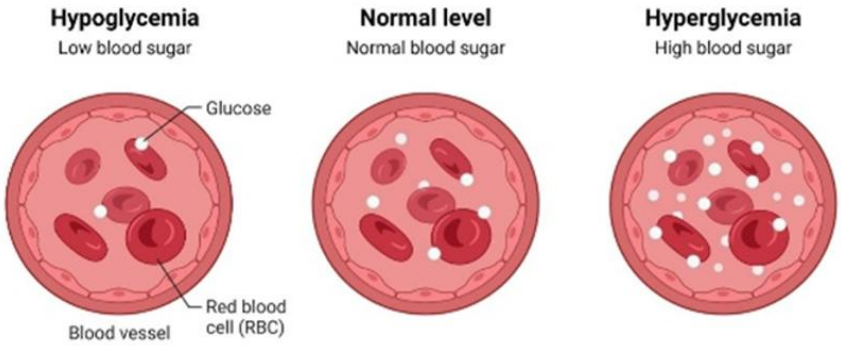

Figure 30: Glucose Molecules in Different Conditions

Types of Diabetes

1. **Type 1 Diabetes Mellitus:** Type 1 diabetes, formerly referred to as insulin - dependent diabetes or juvenile onset diabetes is a kind of autoimmune disease wherein the person's immune system attacks pancreatic beta cells. Consequently, the pancreas secretes extremely small amounts of insulin or no insulin at all. Due to the small amount or no insulin produced, body cells become incapable of receiving glucose to manufacture energy. Type 1 diabetes commonly appears under age 20, but the disorder can occur at any age. Without glucose, body cells must then use fatty acids to synthesize ATP. Stored lipid in adipose tissue is broken down to supply fatty acids. Weight loss also accompanies this depletion of stored triglycerides.

2. **Type 2 Diabetes Mellitus:** Type 2 diabetes, previously known as non-insulin-dependent diabetes mellitus, is the most widespread form of diabetes, impacting more than 90% of individuals diagnosed with the condition. This type of diabetes is characterized by insulin resistance, where the body's cells do not respond properly to insulin, and often, a gradual decline in insulin production. It generally occurs in people who are over 35 years old and obese. The clinical symptoms of this disease are milder, and the glucose levels can be managed through life style changes such as diet, exercise etc. Sometimes medications like glyburid and metformin are use to stimulate release of insulin from the pancreatic beta cells. In some type 2 patients, the pancreas still manufactures and secretes sufficient amounts of insulin, in such patients; diabetes doesn't result from inability to produce sufficient insulin but rather from gradual development of cell resistance to Insulin as a consequence of down-regulation of insulin receptors. [6]

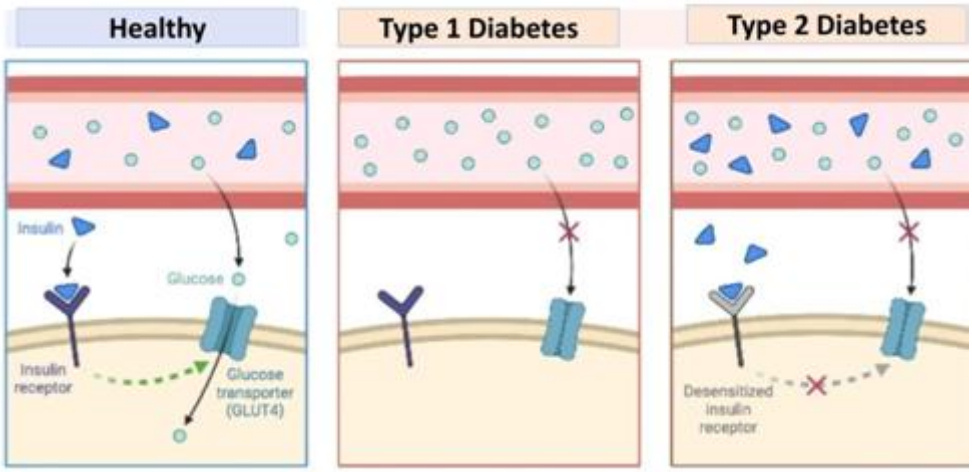

Figure 31: Molecular Basis of Diabetes

3. **Maturity Onset Diabetes (MODY):** MODY is a form of autosomal dominant, monogenic, familial diabetes due to a single gene mutation resulting in dysfunction in pancreatic beta cells. The term MODY was coined by Tattersall and Fajans and stands for maturity onset diabetes. Less than 5% of all the diabetic cases are due to monogenic diabetes. The condition is characterized by high blood glucose level, defected insulin secretion & it's onset between 10 - 40 years of age. This is nonketotic diabetes, having no pancreatic autoantibodies. [7,8]

4. **Gestational Diabetes Mellitus (GDM):** GDM is a metabolic disorder first described by Bennewitz in 1824 in Germany. Characterized by hyperglycemia during pregnancy, this condition was typically recognised in

the 24-28 weeks of gestation. Appropriate management will reduce adverse pregnancy outcomes; however, women diagnosed with GDM are at very high risk for type 2 diabetes, obesity & CVDs. [9,10]

5. **Latent Autoimmune Disease of Adult (LADA):** LADA (Latent Autoimmune Diabetes in Adults) is an autoimmune-associated, slow-progressing form of diabetes that is often referred to as Type 1.5 diabetes. It typically begins in adulthood and lies between Type 1 and Type 2 diabetes in terms of its characteristics. On one end, it shares similarities with insulin-dependent Type 1 diabetes, while on the other, it has features resembling insulin-resistant Type 2 diabetes.

The Immunology for Diabetes Society has specified 3 Criteria for the diagnosis of LADA

- An individual with greater than 30 years of age.
- Autoantibodies to pancreatic beta islets.
- No requirement of insulin for glycemic control in the initial 6 months after diagnosis [11]

Risk Factors

1. **Primary Risk Factor**
   - Family history (first-degree relatives)
   - Age (45+year)
   - Obesity (BMI>30)
   - Physical inactivity
   - Previous history of gestational diabetes in women
   - Polycystic ovarian syndrome (PCOS)

2. **Secondary Risk Factors**
   - Hypertension
   - High cholesterol level
   - Cardiovascular disease
   - Sleep Apnea
   - Stress
   - Smoking
   - Unhealthy diet

Symptoms

Polyuria, polydipsia, polyphagia, fatigue, blurred vision, slow healing of cuts & wound, tingling or numbness in hand or feet etc are the common symptoms appearing in DM.

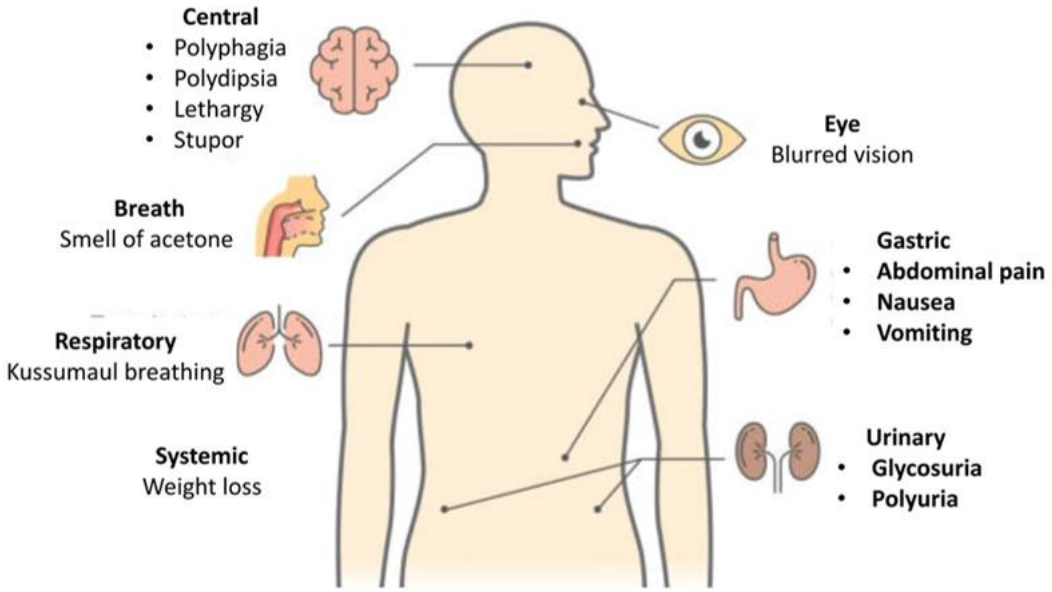

Figure 32: Symptoms of Diabetes

Pathophysiology of DM

The exact mechanism of pathophysiology of Diabetes mellitus is complex & not understood completely. Several different hormones & factors are known to contribute this disease. Glucose is major energy fuel for body cells. On average, fasting blood glucose (before meal) & postprandial (after meal) usually lie between 80 to 100 mg/dl & 120 – 140 mg/dl respectively. A sudden raise in blood glucose level stimulates pancreatic beta cells to secret insulin. Insulin is peptide hormone that reduces blood glucose by activating its influx inside cells. Insufficient & defective insulin secretion, beta cells dysfunction in pancreas leads hyperglycemia. Prolong hyperglycemia leads diabetes mellitus. [12]

IV. COMPLICATIONS

Cardiovascular complications (hypertension, atherosclerosis etc), retinopathies, peripheral vascular disease, cataract, neurological abnormalities, renal

dysfunction, amputations, skin Infections (candida & other fungal infection) etc are some complications appear due to diabetes. [14,15]

Diagnosis of Diabetes Mellitus

The different biochemical tests involved in diagnosis of DM are listed below.

1. **HbA1c:** The HbA1c is Glycosylated hemoglobin, a biochemical test used to monitor patient's glycemic level. HbA1c is useful marker of diabetes & it's complications. Its value determines average glycemic value of 3 months. [15]

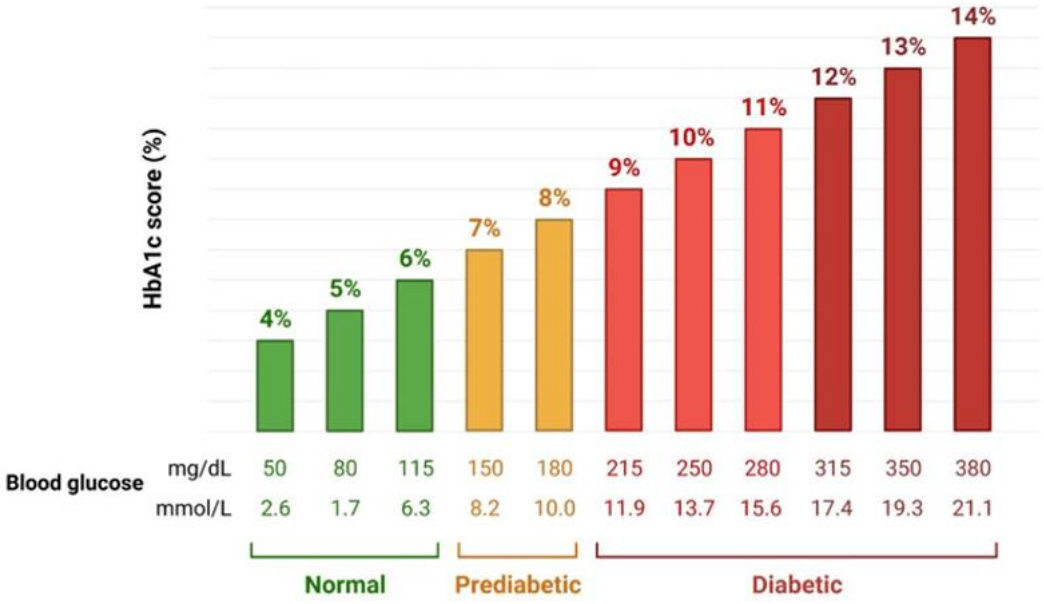

Figure 33: Graphical Representation of HbA1C Level

2. **Glucose Monitoring:** Plasma glucose estimation is useful to monitoring fluctuations of glucose level in response to diet, medications, physical exercise etc. Fasting (before breakfast) & postprandial (after meal) & random estimations are use to diagnose severity of diabetes & it's complications. [16]

3. **C-Peptide:** C-peptide is a useful bio marker to monitor functionality of pancreatic beta cells. It allows discrimination between individuals with type 1 & type 2 Diabetes. [17]

WHO Guidelines for Diagnosing Diabetes Mellitus

According to WHO, any one of the following is sufficient to diagnose diabetes mellitus.

- Blood glucose (Fasting) – ≥126 mg%
- Blood glucose postprandial – ≥200 mg%
- Blood glucose random – ≥ 200 mg% with symptoms [18]

Treatment

According to WHO guidelines, the treatment of DM aims to restore blood glucose level in its normal range, avoid symptoms due to hyperglycemia & other complications. The following medications are useful in treatment of diabetes.

- **Sulfonylureas:** Sulfonylureas was developed by Marcel Janbon in France. They are potassium channel blockers. The main action of sulfonylureas includes the reduction of blood glucose level in type 2 diabetes but not in type 1. Sulfonylureas enhance insulin secretion from pancreas.
- **Nateglinide:** Nateglinide drug is D-phenylalanine derivative manufactured by Ajinomoto, a pharmaceutical industry in Japan. It principally stimulates release of insulin from pancreatic beta cells.
- **Metformin:** Metformin (brand name Glucophage) is first line medication used in DM. Metformin suppress hepatic gluconeogenesis & enhance insulin-mediated uptake of glucose. It promotes peripheral glucose utilization anaerobically. [19]
- **Sitagliptin:** Sitagliptin drug ((Januvia®) is antihyperglycemic drug developed by Merck in 2006. Sitagliptin belongs to gliptin class having dipeptidyl-peptidase 4 inhibitory activity. It is useful in treatment of type 2 Diabetes not controlled by sulfonylureas, metformin or insulin. [20]
- **Insulin therapy:** After the discovery of insulin in early 1920s, people were looked this as a one step towards treatment of diabetes. The patients with insulin therapy require appropriate education on insulin therapy.

Lifestyle Changes

- Weight loss

  Weight loss can improve blood sugar levels and also increase insulin sensitivity.

- Regular exercise approximately 150 minute per week
- Quality of diet [18]

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