Diabetes Mellitus: A Deleterious Metabolic Disorder

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ABSTRACT: Diabetes mellitus is a chronic lifelong disease. It is simply known as diabetes. This metabolic disorder is resulting from a defect in insulin secretion, insulin action or both is called as diabetes mellitus. This condition needs a life stylemanagement, everyday diagnostic and therapeutic limitations. Psychological problems are mostly seen in diabetic patients. It is caused due to biochemical and hormonal imbalances. Due to inappropriate pancreatic insulin secretion or low insulin- directed fastening of glucose by target cells will result in hyperglycemia in blood. This is the main indicator for diabetes mellitus. The course of diabetes is negatively influenced by the comorbid psychological disorders. They are depression, anxiety, cognitive disorders and eating disorders. This article mainly focuses on causes, types, diagnosis, complications and treatment.
Key words: Diabetes mellitus, insulin resistance, epidemiology, etiology, complications, risk factors, insulin, oral hypoglycemic agents

I. INTRODUCTION:

The term "diabetes" was first discovered by Araetus of Cappodocia (81-133AD). Later the "mellitus" was coined by Thomas Willis (Britain) in 1675[1]. Discovery of role of pancreas in diabetes by Joseph Von Mering and Oskar Minkowski in 1889. In 1910, "Sir Edward Albert Sharpey-Schofer of Edinburgh" in Scotland suggested that diabetes lacked a single chemical which produced by pancreas. The name "Insulin" was later proposed by Himsworth, in 1936[2].

The word "diabetes'' was derived from the Greek word meaning "a siphon'', 'go through' and the second word "mellitus" was derived from the Latin word, which means 'honey' or 'sweet'[2].

Diabetes mellitus (DM) is generally called as diabetes. It is a group of diseases characterized by increased levels of glucose in blood resulting from defects in insulin production, insulin action, or both. It is a chronic disease that mainly effects the body condition. It is a disorder that effects the body's ability to make or use insulin. Impaired fasting glycaemia and impaired glucose tolerance are the important risk factors for the future development of diabetes and cardiovascular diseases. In both developed and developing countries diabetes is one of the leading cause of renal failure. It is a metabolic disorder of various causes characterized by chronic hyper glycaemia with disturbances of carbohydrate, fat and protein metabolism. Diabetic ketoacidosis, hyperosmolar hyperglycemic state or death comes under acute complications.[3]

Insulin is a naturally occurring peptide hormone produced by the beta cells of the pancreatic islet; it is considered as the main anabolic hormone of the body. It regulates the metabolism of carbohydrates, fats and protein by elevating the absorption of glucose from the blood stream into liver, fat and skeletal muscle[4].

According to the 2019 data of International diabetes federation,463 million adults are diagnosed with diabetes mellitus. The prevalence was rapidly increasing. In 2017 it is estimated that 425 million people are diagnosed with diabetes mellitus. The prevalence is doubled by 2030 and expected to rise to 629 millions by 2045.This rate is largely reflected by risk factors of obese and gene factors.[3] Diabetes mellitus is common throughout the world and more common in developed countries due to urbanization, lifestyle modification and physical inactivity. Diabetes mellitus is the eighth leading cause of death. 2.2 million deaths were recorded in worldwide due to high blood glucose levels and its associated complications. The prevalence is associated with macrovascular and, microvascular endpoints. 34 millions of Americans were living with diabetes mellitus. Approximately 90-95 % of them were diagnosed with type 2 diabetes mellitus. In 2011,

4.6 millions of people were expired due to diabetes mellitus.[5]

Statistics in percentages and millions:
In 2010 – 285 millions of people were suffering.
In 2019 – 9.3% - 463 millions of people were suffering
By 2030- it is estimated to be 10.2% - 578 millions of people
By 2045- it is estimated to be 10.9%- 700 millions of people
This above estimation may come true, if there is no better control or cure over diabetes mellitus.

Classification of diabetes:
The diabetes is mainly classified into 3 major categories. i.e.,
1.Type 1 diabetes mellitus
2.Type 2 diabetes mellitus
3.Gestational diabetes

Type 1 diabetes mellitus:
Formerly type 1 diabetes mellitus is also known as Insulin Dependent Diabetes Mellitus (IDDM)(or) Juvenile diabetes (or) Young onset diabetes.

Diabetes mellitus is the most common endocrine disorder. Type 1 diabetes mellitus is a T cell mediated autoimmune disorder which our immune system attacks beta cells which are used to produce insulin. Insulin insufficiency occurs due to destruction of pancreatic beta cells which causes hyperglycemia and a proportion to ketoacidosis. Type 1 diabetes mellitus is caused due to lack of insulin. People with type 1 diabetes mellitus cannot produce insulin by their own. Currently, once diagnosed, type 1 diabetes is a life long disease which cannot be cured but can be controlled by taking the pharmacological treatment and proper diet. Both genetic and environmental factors are the causes for the type 1 diabetes mellitus. Diabetes is identified or diagnosed by testing the glycated hemoglobin (HbA1C) or the level of sugar in the blood stream. Type 1 diabetes mellitus can be differentiated from type 2 diabetes mellitus by testing for the existence of autoantibodies. Insulin is needed for the production of energy by allowing sugar to move from the bloodstream into the cells[6]. Type 1 diabetes is also known as 'Juvenile' diabetes because it is mainly seen in children and young people. People with type 1 diabetes are insulin-dependent, which means they have to take insulin to maintain their blood glucose levels in normal[7].

Type 2 diabetes mellitus:[7]
Formerly type 2 diabetes mellitus is also known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM) (or) Adult onset.

Type 2 diabetes mellitus is mostly seen in adults, so it is also called as 'Adult onset' diabetes mellitus. Type 2 diabetes mellitus is most common and a chronic disease, it is a lifelong disease. Middle aged people and elder people are mostly diagnosed with this type 2 diabetes mellitus. In some cases, type 2 diabetes mellitus is effecting the kids and teenagers because of childhood obesity.[4] In type 2 diabetes mellitus, the insulin cells does not use sugar levels properly to produce enough energy to maintain the proper functioning of the body. Mainly 6 factors are involved in type 2 diabetes mellitus are 1. Genes, 2. Overweight, 3. Metabolic syndrome, 4. Too much glucose from your liver, 5. Bad communication between cells, 6. Broken beta cells. In type 2 diabetes mellitus, beta cells cannot produce enough insulin for body metabolism or our body cells cannot respond to insulin as well. This type 2 diabetes mellitus can lead to several symptoms and severe complications due to high blood glucose levels.[6] Now a days, many people are diagnosed with type 2 diabetes mellitus due to decreased physical activity, increased blood pressure and improper diet. By having the healthy diet and exercises they can control their blood glucose levels. The important factor for type 2 diabetes mellitus is weight loss.

Gestational diabetes mellitus:[7]
Gestational Diabetes Mellitus (GDM) is defined as any degree of impaired glucose tolerance with onset or first recognition during pregnancy.

Gestational diabetes is typically develops in the second or third trimester of pregnancy. It mainly occurs when body becomes less sensitive to insulin. It is not seen in all women and it resolves after giving birth to the baby. People diagnosed with gestational diabetes are at a higher risk for developing type 2 diabetes mellitus in their later life.
In gestational diabetes:
Normal range of FBS: < 95 mg/dl
Normal range of PPBS: <125 mg/dl

Etiology:[8]
➢ Decline in pancreatic beta cell function
➢ Destruction of beta cells
➢ Decreased beta cell mass

➢ Obese
➢ Combination of genetic susceptibility
➢ Environmental factors
➢ Buildup of glucose in bloodstream
➢ Increased absorption of glucose
➢ Genetic factors
➢ Viral infections
➢ Precipitating factors

Clinical Manifestations:
Symptoms caused due to increased blood glucose levels.

General symptoms:
Increased thirst (Polydipsia),increased hunger (Polyphagia)**,** weight loss,frequent urination (Polyuria)**,** blurred vision**,** fatigue, delayed wound healing, tiredness,lack of sleep (Insomnia),increased cholesterol, presence of ketones in urine, burning, pain and numbness on feet,skin and vaginal infections,gum infections, dry mouth, tingling sensation in hands, irritability.[9]

Common symptoms in Men:
Erectile dysfunction,poor muscle strength and muscle growth**,** low testosterone[10]

Common symptoms in women:
Urinary tract infections, dry skin, itchy skin**,** frequent urination[11]
Risk factors:[12]
a.   **Modifiable factors:**
Increased body mass index, physical inactivity, poor nutrition, hypertension, smoking, alcohol
b.   **Non modifiable factors:**
Age**,** race, family history,low birth weight, ethnicity
c.   **Psychosocial factors:**
Depression, increased stress**,** poor mental status, low social support
d.   **Others:**

Gestational diabetes,poly cystic ovarian syndrome,insulin resistance,abnormal cholesterol and triglyceride levels

Pathogenesis:
A Schematic representation ofType 1 diabetes mellitus:[13]

Viral infection
↓
Immune response against beta cells
↓
Alteration of pancreatic beta cells
↓
Beta cell injury
↓
Autoimmune destruction of beta cells
↓
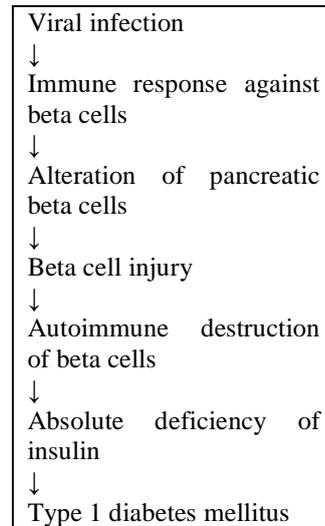Absolute deficiency of insulin
↓
Type 1 diabetes mellitus

Figure 1: A Schematic representation of type 1 diabetes mellitus (Courtesy from Nushrat Parveen et al)

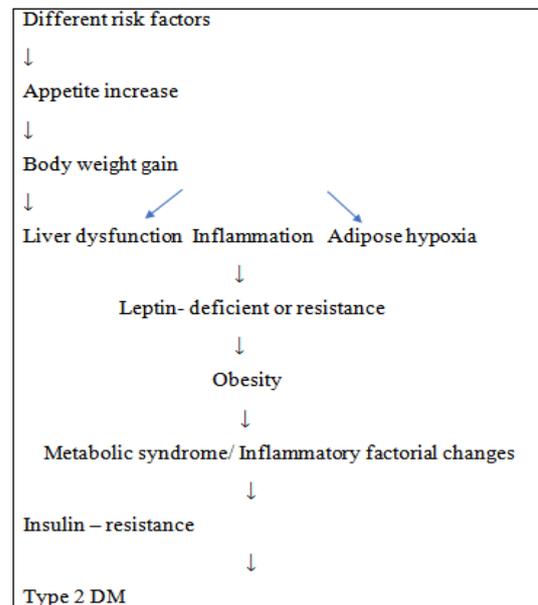**A Schematic representation of Type 2 diabetes mellitus:[14]**

Different risk factors
↓
Appetite increase
↓
Body weight gain
↓
Liver dysfunction Inflammation Adipose hypoxia
↓
Leptin- deficient or resistance
↓
Obesity
↓
Metabolic syndrome/ Inflammatory factorial changes
↓
Insulin – resistance
↓
Type 2 DM

Figure 2: A Schematic representation of type 2 diabetes mellitus (Courtesy from Da-Yong Lu et al)
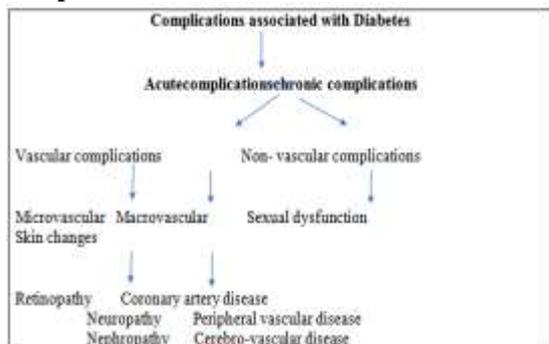
Complications:[15]

Figure 3: Complications associated with diabetes mellitus and their pathogenesis (courtesy from Shivkant M. Kide et al)

VASCULAR COMPLICATIONS:
Microvascular complications:[16]
Diabetic Neuropathy: It is a condition which mainly damages the nerve tissues due to increased blood glucose(sugar) levels. In diabetic neuropathy, legs and feet are mainly affected. Symptoms were mild to moderate in some people; debilitating, painful and even fatal in some people.[16]
DiabeticRetinopathy: Diabetes is the most common cause of blindness in adults. In India, nearly 1 million cases are diagnosed in a year. It is a condition that affects the eyes. It is a disease of retina caused by microangiopathy due to long term effect of diabetes leading to progressive damage of retina and blindness.[17]
Diabetic Nephropathy: It is a common complication of type 1 and type 2 diabetes. It is a serious kidney-related complication seen in both type 1 and type 2 diabetes. It is also known as diabetic kidney disease. About 25% of people suffering with diabetes develops kidney related issues. It is mainly affects the functioning of kidneys. This condition can be controlled by having treatment but cannot be cured.[18]
Macrovascular complications:[16]
Coronary artery disease: Coronary artery disease is a condition which mainly effects the heart's major blood vessels. Chest pain and heart attack are mainly seen in this condition. In India, more than 10 million cases were recorded in every year. By the build of plaque, coronary arteries become narrow or blocked so that blood flow becomes abnormal.
Peripheral artery disease: This is a condition in which the blood flow is reduced to the limbs due to narrowed blood vessels. Peripheral artery disease is also called as Peripheral vascular disease. Fatty

deposits and calcium building up in the walls of the arteries are the symptoms seen in this condition. This condition is known as atherosclerosis.
Cerebral vascular disease: It is a condition or disorder that mainly affects the blood vessels and decreased blood supply to the brain. Vascular malformation, transient ischemic attack, aneurysm and stroke comes under the cerebrovascular disease. Symptoms of this condition is based on the location of the blockage and its impact on brain tissues. Loss of vision, paralysis, loss of balance are the symptoms of this condition.

Non vascular complications:[19]
➢ Skin changes
➢ Loss of hearing
➢ Gastroparesis
➢ Infections
➢ Sexual dysfunction

Diagnosis:
Type 1 and type 2 diabetes mellitus is diagnosed by based on their symptoms, age and blood tests;
a. **FASTING BLOOD SUGAR(FBS):** The FBS is a test used for measuring the blood glucose levels.Blood is collected in the early morning after fasting overnight. This test requires at least 12 hours fast. Normally, the fasting blood glucose levels ranges from 70-100mg/dl (5.6 mmol/L). The blood glucose levels ranging between 110-125mg/dl is called as impaired fasting glucose (i.e., Prediabetes). The blood glucose levels ranging greater than 126mg/dl on two or more samples is considered as diabetes.[20]
b. **RANDOM BLOOD SUGAR(RBS):** The RBS is the test used to measure the blood glucose levels. The blood sample is collected at a random time. It helps to assess the management of blood glucose levels. Regardless of having any food or liquid, a blood sugar levels of 200 mg/dL and 11.1mmol/L or higher are considered as diabetes.[21]
c. **ORAL GLUCOSE TOLERANCE TEST:** The oral glucose tolerance test is used to measure the blood glucose levels. For this test, the person has to fast overnight, and then the fasting blood sugar level is measured.[22] After having a meal or a sugary liquid, the blood sugar levels are tested periodically for next 2 hours. It quickly determines the insulin resistance and impaired beta cell

functioning.[21]A blood sugar level less than 140mg/dL (7.8mmol/L) is considered to be normal. A range more than 200 mg/dL(11.1mmol/L) is considered as diabetes. The range between 140 and 199 mg/dL(7.8mmol/L and 11.0mmol/L) determines prediabetes.[9]

d. GLYCATED HAEMOGLOBIN (A1C) TEST: This test calculates the percentage of blood sugar levels attached to hemoglobin and the oxygen carrying protein in red blood cells. It determines the average blood glucose levels from past 2-3 months and it doesn't requires any fasting. The higher blood sugar levels, the more amount of sugar is attached to the hemoglobin. An A1C level < 5.7% is considered as normal. An A1C level between 5.7- 6.4% determines the prediabetes. An A1C level of 6.5% or more on two different tests is considered as diabetes[23].

Management:
Treatment for type 1 diabetes mellitus:[24]
Treatment for type 1 DM includes:

➢ Intake of insulin

➢ Frequent blood sugar monitoring

➢ Taking healthy diet

➢ Maintain proper weight

➢ Physical activity

Insulin therapy:
        People with type 1 diabetes mellitus requires insulin replacement and they are in need of taking multiple daily injections (MDI) of basal and prandial insulin. Different varieties of insulins (basal and prandial) and different routes of administration (syringe, pen, prefilled pen, pump) are available. To attain ideal glycemic control by avoiding hypoglycemia and adverse effects such as excessive weight gain and lipodystrophy requires insulin intake by monitoring the glucose.[25] Basal insulins includes long-acting insulins and intermediate-acting insulins and they are given 1-3 times a day to control their blood glucose levels. Prandial insulins includes rapid acting insulins and short acting insulins and these are taken by a patient before each meal. Mostly these insulins are given 3 times a day before the main meal and given if more than 3 meals per day are taken.[26]

Insulin and other medications:
People suffering from type 1 diabetes depends on insulin for the lifetime.
• Short -acting (regular) insulin

• Rapid -acting insulin
• Intermediate-acting insulin (NPH)
• Long-acting insulin

Short-acting insulin(regular): These are mainly used to treat type 1 diabetes mellitus but in rare cases used to treat type 2 diabetes mellitus in hyperglycemia conditions. This shows action within 15 to 30 min and lasts from 1 to 12 hours.[25]
Ex: Humulin R, Novolin R
Rapid-acting insulin: These insulins reach their peak plasma concentrations with in 30-90 mins.
Ex: Insulin glulisine (Apidra), Insulin lispro (Humalog), Insulin aspart (Novolog)
Long-acting insulin: Onset of action is 3 to 4 hours and their maximum duration of action is 20 to 24 hours.[26]
Ex: Insulin glargine (Lantus, Toujeo, Solostar)
Intermediate-acting insulin: Onset of action is 1-2 hours and their maximum duration of action is 4-14 hours.[27]
Ex: Insulin NPH (Novolin N, Humulin N)
Treatment for type 2 diabetes mellitus:[28]
Treatment for type 2 diabetes includes:

➢ Frequent blood sugar monitoring

➢ Exercising regularly

➢ Weight loss

➢ Proper diet

➢ Pharmacological treatment includes drugs and insulin
Possible medication for type 2 diabetes includes:

BIGUANIDES:
METFORMIN: Metformin is the first-line drug for type 2 diabetes mellitus and comes under the brand name of Glucophage.It belongs to the class of biguanides. It helps to maintain proper body's response towards insulin. Metformin decreases the production of sugar from liver that which stomach/intestine absorbs. Combination of Metformin and insulin can be used in type 2 diabetes, but it cannot be used in the treatment of type 1 diabetes.Metallic taste, asthenia, heartburn, stomach upset, diarrhea are the most common side effects.[29]
Ex: Metformin(dimethylbiguanide), Phenformin (phenethylbiguanide), Buformin (butylbiguanide)
SULFONYL UREAS: Sulfonylureas are a class of drugs used in the treatment of type 2 diabetes mellitus. Sulfonylureas stimulates secretion of insulin from pancreatic beta cells and are used for the treatment of type 2 diabetes mellitus. It works effectively by decreasing blood sugar levels. These

category is mainly used in the treatment of type 2 diabetes mellitus. Hypoglycemia, weight gain, skin rash, sweating, dizziness are the most commonly caused side effects.[30]

Ex: Glipizide(glucotrol),Glimepiride(amaryl),
Tolinase (tolazamide)

Tolbutamide (Tolvex)

Dipeptidyl-Peptidase (Dpp-4) Inhibitors: DPP-4 inhibitors are new class of antidiabetic drugs. DPP-4 inhibitors are used as second and third linedrugs for treatment of type 2 diabetes. It blocks the dipeptidyl peptidase 4 enzyme. It lowers the blood glucose levels by reducing appetite.Pancreatitis, sore throat, purple rash, runny nose, stomach pain are the commonly seen side effects in many people.[31]

Ex: Sitagliptin (Januvia), Teneligliptin (Tenelia), Saxagliptin (Onglyza),

Vildagliptin (Amivilda), Linagliptin (Ondero, Trajenta), Alogliptin (Nesina)

ALPHA-GLUCOSIDASE INHIBITORS: These are considered as Starch blockers. These class of drugs are used to decrease the post meal blood glucose levels. Insulin secretion and insulin sensitivity are not directly effected by the alpha glucosidase inhibitors. It slow down the process of carbohydrate digestion. These drugs mainly interfere with digestion of carbohydrates for achieving better blood sugar levels.Side effects includes increased colonic gas production, bloating, mild diarrhea.[32]

Ex: Voglibose (Vogli), Acarbose (Precose), Miglitol (Glyset)

THIAZOLIDINEDIONES: Thiazolidinediones are the class of drugs used in the treatment of type 2 diabetes. These drugs increases the insulin sensitivity. These drugs are not used in first choice treatment, because these drugs are having many side effects.These drugs mainly blocks the production of glucose from the liver.Thiazolidediones are the anti-diabetic drugs mainly used for treating the insulin resistance.Weight gain, fractures, heart failure are the commonly seen side effects.[33]

Ex: Pioglitazone (Actos), Rosiglitazone (Avandia)

MEGLITINIDES: Meglitinides are the oral hypoglycemic drugs used to treat type 2 diabetes mellitus. They function by triggering the insulin production. These drugs mainly binds to ATP sensitive K+channels and promotes the secretion of insulin and decreases the blood sugar levels. Meglitinides are the short-acting oral hypoglycemic drugs and it has a major role in lowering post prandial hyperglycemia and decreases the risk of

hypoglycemia.[34]Headache, weight gain, dizziness, hypoglycemic effects are the mostly commonly caused side effects.[34]

Ex: Nateglinide (Starlix), Repaglinide (Prandin)

Treatment for Gestational diabetes:[35]

By controlling blood sugar levels, we can keep baby healthy and we can avoid further complications during delivery. In addition, taking a proper diet and doing exercises are also hypoglycemic medications.

Doctor will monitor the blood sugar levels during labor. If blood sugar levels increases, baby will release high levels of insulin which may lead to decreased blood sugar levels right after birth.

Prevention of diabetes:

Preventing type 1 diabetes is impossible because it is caused due to problem associated with the immune system.[36]

The relation between the type 2 diabetes mellitus and risk factors (overweight, improper diet, physical inactivity and usage of tobacco) is equivalent in all regions of the world.

If a patient is diagnosed with prediabetes, there are some things that can be delayed or prevent in getting type 2 diabetes mellitus.[37]

1.By doing physical activity for at least 150 min per week.

2.Have small portions of meal.

3.Avoid saturated foods and trans fat in your diet.

4.Maintain healthy weight.

II. CONCLUSION:

Diabetes mellitus is a fast growing disease which is increasing day by day globally. Incidence of diabetes is increasing due to stress and improper diet. If untreated, it leads to multiple complications (i.e., loss of vision, kidney damage, nerve damage). The regular physical activity not only helps in control of blood sugar levels, but also helps in control of body weight and blood pressure which lowers bad cholesterol. The risk is two times more for women when compared to men with type 1 diabetes. Diabetic complications are complex and multi directional based on pathophysiological mechanism. This review explores the terms of historical perspective, biochemical basis, economic burden, management interventions along with future perspectives. treatments known from middle ages and the annotations of its pathogenesis mainly occurred in 20th century.

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