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A Review on Diabetes Mellitus

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Abstract

Diabetes is a life-long disease that affects the way your body handles glucose, a kind of sugar, in your blood. It is often referred as Diabetes Mellitus (DM) by doctors which describes a group of metabolic diseases resulting in high blood glucose, either due to inadequate production of insulin or because the body's cells do not respond well to insulin or both. Normally, the pancreas releases insulin to help your body store and use the sugar and fat from the food you eat. Diabetes can occur when the pancreas produces very little or no insulin, or when the body does not respond appropriately to insulin. In 2014 it was estimated that over 422 million people throughout the world had diabetes. The most common diabetes symptoms include frequent urination, intense thirst and hunger, weight gain, unusual weight loss, fatigue, cuts and bruises that do not heal, male sexual dysfunction, numbness and tingling in hands and feet. According to health day reporter, Steve Reinberg in September 2018, 30 million Americans now have diabetes. 1 in 7 Americans has diabetes, and many don't even know they have high blood glucose disease. According to the U.S. centers for disease control and prevention, 14% of U.S adults have diabetes of which 10% know it and over 4% are undiagnosed. According to the American Diabetes Association, 95% of the diabetes cases are type 2, which is often tied to overweight or obesity. About 5 % of diabetes cases are type 1, which can arise early in life and is not linked with lifestyle factors. According to the report, nearly 16% of men and 12% of women have diabetes and the risk of developing both diagnosed and undiagnosed diabetes increases with age. In terms of population, diabetes is more common among Hispanics (20%), and blacks (18%), than whites (12%). The research found that overweight and obese are more likely to develop diabetes. Only 6% of underweight or normal weight adults had the disease, while 12% of overweight adults and 21% of obese adults had diabetes. Diabetes cannot be cured but treatment modalities include lifestyle modifications, treatment of obesity, and oral hypoglycemic agents like iguanids, sulfonylurea, thiazolidinedione's, alpha glucosidase inhibitors, dipeptidyl peptidase-IV inhibitors and insulin.

Keywords: Diabetes; Hyperglycemia; Hypoglycemia; Diabetes mellitus

Introduction

Diabetes Mellitus (DM) is an endocrinological disorder which is a group of metabolic or heterogeneous affliction resulting from an irregularity in insulin secretions and insulin actions or both. It is one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago. It is also referred as black-death from the 14th century. Patients with diabetes have been classified into two main categories: type-1 diabetes mellitus (T1DM), characterized by a near-absolute deficiency of insulin secretion and type-2 diabetes mellitus (T2DM) where the cause is a combination of insulin resistance and an insulin secretory defect. In 1936, the distinction between type 1 and type 2 diabetes mellitus was clearly made. Type 2 diabetes mellitus was first described as a component of metabolic syndrome in 1988. The presence of DM shows increased risk of many complications such as cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, retinopathy, blindness, amputations, etc. People living with

type 2 DM are more vulnerable to various forms of both short and long term complications, which often lead to their premature death. Drugs are used primarily to save life and alleviate symptoms. Secondary aims are to prevent long-term diabetic complications and, by eliminating various risk factors, to increase longevity.

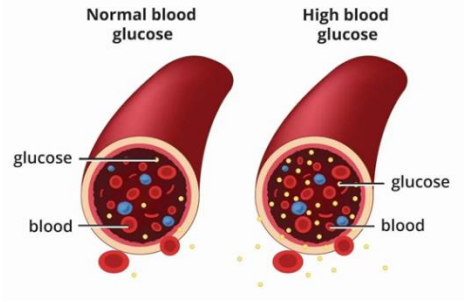

Figure 1: *Illustration of an artery with normal blood glucose level and an artery with high blood glucose levels. (Image source: foodnurish.com.*

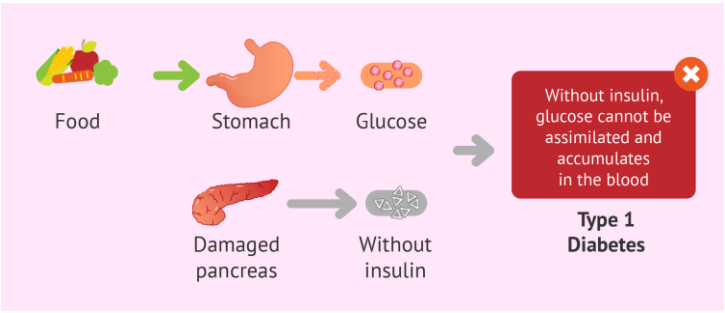

Figure 2: *(Image source: babygest.com).*

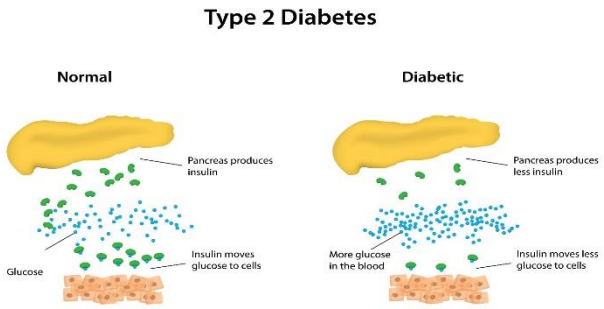

Figure 3: *(Image source: thermofisher.com).*

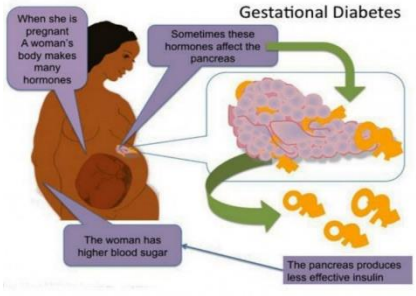

Figure 4: *(Image source: danii.org.au).*

Epidemiology of Diabetes

Globally, the number of people with diabetes mellitus has quadrupled in the past three decades, and diabetes mellitus is the ninth major cause of death. Most patients with T2DM have at least one complication, and cardiovascular complications are the leading cause of morbidity and mortality in these patients. The number of people (20-79 years) living with diabetes in 2017 was estimated to be 424.9 million. This value is further estimated to be 628.6 million by 2045. The largest number of people (20-79 years) with diabetes are in China, India and United States in 2017. Diabetes in people older than 65 years was estimated to be 122.8 million in 2017, which is further estimated to be 253.4 million in 2045. It was estimated that globally as many as 212.4 million people or half (50.0%) of all people 20-79 years with diabetes were unaware of their disease in 2017. In low income countries like Africa, the proportion of undiagnosed diabetes is 69.2% while in high income countries, this value contributes to 37.3%. Asia is a major area of the rapidly emerging T2DMglobal epidemic, with China and India the top two epicenters.

Types of Diabetes Mellitus

Earlier Diabetes was classified mainly into two types as Type 1 or Insulin-Dependent Diabetes Mellitus (IDDM) and Type 2 or Non-Insulin-Dependent Diabetes Mellitus (NIDDM) which were proposed by WHO in 1980 and 1985. In recent years, the traditional way of classifying DM has been replaced by new classification which includes mainly four types of DM.

I. Type 1 Diabetes Mellitus
   A. Autoimmune
   B. Idiopathic

II. Type 2 Diabetes Mellitus

It ranges from relative insulin deficiency to disorders of insulin secretion and insulin resistance.

III. Gestational Diabetes Mellitus (Occurs in Pregnant woman)

IV. Other specific types of Diabetes Mellitus
   A. Genetic defects in β-cell function
      1. Chromosome 12, HNF-1α (MODY 3)
      2. Chromosome 7, glycosidase (MODY 2)
      3. Chromosome 20, HNF-4α (MODY 1)
      4. Mitochondrial DNA
      5. Monogenic Diabetes
   B. Genetic defects in insulin action
      1. Type A insulin resistance
      2. Leprechaunism
      3. Rabson-Mendenhall syndrome
      4. Lipotrophic diabetes
   C. Disease of the exocrine pancreas
      1. Pancreatitis
      2. Pancreatectomy/trauma

3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalcificpancreatopathy

D. Endocrinopathies
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma

E. Pharmacologically or chemically induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormones
6. Diazoxide
7. B-adrenergic agonists
8. Thiazides
9. Dilantin (phenytoin)
10. α-interferon

F. Others
1. Infections
    1. Congenital rubella
    2. Cytomegalovirus
    3. Others
2. Infrequent forms of autoimmune diabetes
    1. Stiff-man syndrome
    2. Antibodies against insulin receptors
    3. Others
3. Other syndromes occasionally associated with diabetes
    1. Down's syndrome
    2. Klinefelter's syndrome
    3. Turner's syndrome
    4. Wolfram's syndrome
    5. Friedreich's ataxia
    6. Huntington's chorea
    7. Lawrence-Moon-Biedel syndrome
    8. Myotonic dystrophy
    9. Porphyria
    10. Prader-Willi syndrome

G. Post-Transplant

Type 1 Diabetes Mellitus

It is also known as insulin-dependent diabetes or juvenile-onset diabetes (because it often begins in childhood). It is an autoimmune condition characterized by beta cell destruction. Thus, the damaged pancreas doesn't make insulin. It may also be caused by a genetic predisposition.

Patients with type 1 diabetes are associated with a number of medical risks such as:

1. Diabetic Retinopathy (damage to the tiny blood vessels in eyes)
2. Diabetic Neuropathy (damage to the nerves) and
3. Diabetic Nephropathy (damage to the kidneys)

Serious conditions like risk of heart disease and stroke may also arise in such patients. All type 1 diabetic patients require insulin therapy to maintain normal blood glucose level. Insulin can be injected through the skin into the fatty tissue below by the following methods:

- Syringes
- Insulin pens that use pre-filled cartridges and a fine needle
- Jet injectors that use high pressure air to send a spray of insulin through the skin
- Insulin pumps that dispense insulin through flexible tubing to a catheter under the skin of the abdomen

A doctor generally prescribes for A1C blood test which estimates the blood sugar levels over the previous three months. This test provides information about how well the blood sugar level is controlled and doctors can easily identify the risk of complications. Following activities are advised in case of type 1 diabetes.

- Proper diet plan (Dietician or doctors can advise about meal plan)
- Regular exercise
- Frequent testing of blood sugar levels
- Taking insulin and other medications as per doctor's advise

Type 2 diabetes mellitus

It is also known as non-insulin dependent or adult onset diabetes. However, over the past 20 years, this has become common in children and teens because of overweight and obesity. Type 2 diabetes is more common than type 1 and accounts for 90% of the total diabetes cases throughout the world. This type of diabetes effects the use of glucose for energy by the body. It stops the body from using insulin properly, which results in high blood sugar level if not treated on time.

In type 2 diabetes, insulin resistance occur because the insulin secreted by the pancreas is not enough to maintain the blood sugar level. Insulin resistance usually happens in fat, liver and muscle cells. Both fasting and post prandial plasma glucose concentration is increased. The normal glucose homeostasis cannot be maintained due to insufficient concentration of plasma insulin. Over a period of time, this results in beta cell failure which results in insulin deficiency in the body. Insulin resistance happens by

several factors such as obesity, improper diet, hormonal imbalances, lack of physical activity, genetics and long term use of certain medications like HIV/AIDS medications and corticosteroids.

Table 1: *Top 10 countries for number of people with diabetes (20-79 years), 2017 and 2045.*

2017			**2045**		
Rank	**Country/Territory**	**Number of people with Diabetes (Million)**	**Rank**	**Country/Territory**	**Number of people with Diabetes (Million)**
1.	China	114.4	1.	India	134.3
2.	India	72.9	2.	China	119.8
3.	United States	30.2	3.	United States	35.6
4.	Brazil	12.5	4.	Mexico	21.8
5.	Mexico	12.0	5.	Brazil	20.3
6.	Indonesia	10.3	6.	Egypt	16.7
7.	Russian Federation	8.5	7.	Indonesia	16.7
8.	Egypt	8.2	8.	Pakistan	16.1
9.	Germany	7.5	9.	Bangladesh	13.7
10.	Pakistan	7.5	10.	Turkey	11.2

Table 2: *People living with diabetes (20-79 years) who are undiagnosed per region, 2017.*

Rank	**International Diabetes Federation (IDF) region**	**Proportion Undiagnosed (%)**	**Number of people with undiagnosed diabetes (million)**
1.	Africa	69.2	10.7
2.	South-East Asia	57.6	47.2
3.	Western Pacific	54.1	85.9
4.	Middle East and North Africa	49.0	19.0
5.	South and Central America	40.0	10.4
6.	Europe	37.9	22.0
7.	North America and Caribbean	37.6	17.3

Table 3: *Test results for diagnosis of diabetes and prediabetes.*

Diagnosis	**A1C**	**Fasting Plasma Glucose**	**Oral Glucose Tolerance Test**	**Random Plasma Glucose Test**
Normal	below 5.7%	99 mg/ dl or below	139 mg/ dl or below	N/A
Prediabetes	5.7% to 6.4%	100 to 125 mg/ dl	140 to 199 mg/ dl	N/A
Diabetes	6.5% or above	126 mg/ dl or above	200 mg/ dl or above	200 mg/ dl or above
(Source: American Diabetes Association)				

Table 4: *Types of Oral antidiabetics.*

S. No.	**Class**	**Examples**	**Mechanism of Action**
1.	Alpha Glucosidase inhibitors	Acarbose, Miglitol and Voglibose	They work by slowing down the digestion of carbohydrates, which in turn prevents blood glucose from rising too fast after meals.

2.	Biguanides	Metformin	These drugs wok by preventing the production of glucose in the liver and reducing the amount of sugar absorbed by the intestines. Metformin is commonly used as first-line treatment for type 2 diabetes.
3.	Bile acid sequestrants or bile acid resins (BARs)	Colestipol, Colesevelam and Cholestyramine	These drugs lower the cholesterol level.
4.	Dopamine-2 agonists	Bromocryptine	These drugs reset the hypothalamic circadin rhythm, which obesity can effect. This reset helps reverse insulin resistance and causes a decrease in glucose production in the liver.
5.	DPP-4 inhibitors or gliptins	Sitagliptin, Linagliptin, Vildagliptin, Saxagliptin and Alogliptin	These drugs help improve blood sugar levels by preventing the breakdown of GLP-1 by blocking the enzyme dipeptidyl peptidase-4.
6.	Meglitinides	Repaglinide and Nateglinide	Stimulate the pancreas to release insulin.
7.	SGLT2 inhibitors (Sodium Glucose Transport Protein 2)	Canagliflozin, Dapagliflozin and Empagliflozin.	These are the drugs which lowers blood glucose levels by excreting the excess glucose in urine.
8.	Sulfonylureas	Glimepiride, Glyburide and Glipizide	They stimulate pancreas to release insulin in order to reduce the blood glucose levels.
9.	Thiazolidinediones	Rosiglitazone and Pioglitazone	They work by reducing the glucose production in the liver.

Table 5: *Types of Insulin used to treat type 2 diabetes are as below.*

Type	Time to take effect	Duration
Rapid-acting	About 15 minutes with peak in 1 hour	2 – 4 hours
Short-acting (Regular)	About 30 minutes with peak in 2 – 3 hours	3 – 6 hours
Intermediate-acting	About 2 to 4 hours with peak in 2 – 4 hours	12 – 18 hours
Long-acting	About hours after injection with no peak	24 hours or longer

Following activities are advised in case of type 2 diabetes.

- Proper diet plan (Dietician or doctors can advise about meal plan)
- Regular exercise
- Frequent testing of blood sugar levels
- Taking oral medications as per doctor's advice

Common symptoms of type 1 and type 2 diabetes

- Feeling more thirsty than usual
- Frequent urination
- Weight loss without exercise
- Blurred vision
- Feeling tired and weak
- Presence of ketones in urine
- Slow healing of cuts and wound
- Mood changes or feeling irritable
- Getting a lot of infection, such as gum, skin and vaginal infections
- Many patients with type 2 diabetes are asymptomatic, and they are often diagnosed with type 2 diabetes when routine measurements reveal high blood glucose concentrations.

Gestational Diabetes

It is also known as pregnancy induced diabetes. It is a temporary condition in which the blood glucose levels increase during third

trimester of pregnancy but usually return to normal after delivery. According to Centers of Disease Control and Prevention (CDC), between 2 – 10% pregnancies each year results in gestational diabetes. Women with gestational diabetes are at an increased risk of complications during pregnancy and at delivery. These women and their children are possibly at an increased risk of type 2 diabetes in the future. According to CDC report, around 50% of people with gestational diabetes will later develop type 2 diabetes.

Complications associated with Gestational diabetes

Uncontrolled or untreated blood sugar levels can cause problems to babies as well as their mother. Most women with gestational diabetes deliver healthy babies if proper treatment is given.
Complications in baby can be of the following types.

- **Low blood sugar**: Babies may be hypoglycemic shortly after their birth because their own insulin production is high.
- **Premature birth**: Gestational diabetes increases the risk of mothers giving premature birth.Excess growth: High glucose levels in mother can cross the placenta which can trigger the baby's pancreas to make extra insulin. This in turn, can cause the baby to grow too large. As a result of this, it may require a C-section.
- **Death**: If the gestational diabetes is left untreated, it may result in the death of the baby before delivery or shortly after delivery.
- **Type 2 Diabetes later in life**: Mothers with gestational diabetes are at a higher risk of developing type 2 diabetes later in their life. The same applies to their babies.

Following activities are advised in case of gestational diabetes.

- Proper diet plan (Dietician or doctors can advise about meal plan)
- Regular exercise
- Staying active
- Monitoring blood sugar levels
- Monitoring the growth and development of the fetus
- Keeping weight gain under control
- Taking oral medications or insulin as per doctor's advice to control blood sugar level

Diagnosis of Diabetes

Diabetes and Prediabetes can be diagnosed by several methods by a doctor or a registered healthcare practitioner. Doctors general recommend different tests depending on whether the patient has any symptoms or not, or if the patient is pregnant. Diagnosis at an early stage can be accomplished through relatively inexpensive blood glucose test. The blood test may be repeated on a second day to diagnose diabetes on recommendation of a doctor. However, if your blood glucose level is very high, or if you have classic symptoms of hyperglycemia in addition to one positive test, second test may not be required by the doctor to diagnose diabetes (Tables 1-5) (Figures 1-4).

1. Fasting Plasma Glucose Test (FPG): In this test, the patient should not eat or drink anything except water for at least 8 hours. The patient is advised to have a normal dinner and then undergo fasting overnight. The test is done next day in the morning before having breakfast.
2. A1C Test: In this test, the average blood glucose for the past two to three months is measured. This test is also called hemoglobin A1C, HbA1C, glycated hemoglobin, and glycosylated hemoglobin test. This test has an advantage over other tests because the patient does not have to undergo fasting or drink glucose before test.
3. Oral Glucose Tolerance Test (OGTT): You will have to fast for at least 8 hours before this test. Blood sample is taken to measure the glucose level after fasting and then you are allowed to drink a liquid which is high in sugar. After 2 hours of drinking the liquid, another blood sample is withdrawn to check the glucose level in blood.
4. Random plasma glucose test: In this test, blood glucose can be tested anytime of the day without fasting.
5. Glucose challenge test: This test is done to check gestational diabetes in pregnant woman. Fasting is not required for this test. The patient is given a sweet liquid containing glucose to drink. Blood sample is taken after one hour of drinking sweet liquid to measure the blood glucose content. If the blood sugar level is too high, oral glucose tolerance test after fasting will be done to confirm gestational diabetes.

Screening of Diabetes

There is a guideline developed by American Diabetes Association (ADA) which recommends screening of following people for diabetes.

- Anyone with a BMI (Body Mass Index) higher than 25 (23 for Asian Americans), regardless of age, if they have any additional risk factors like sedentary lifestyle, high blood pressure, high cholesterol level, a history of polycystic ovary syndrome, heart disease or family history of diabetes.
- Any person older than 35 years of age should have their blood sugar tested. If the results are normal, screening can be done every 3 years after that.
- Women with gestational diabetes should be screened for diabetes every 3 years.
- Anyone who has been diagnosed with prediabetes should undergo screening every year.
- HIV positive patients are advised to go for regular screening

Prevention of Diabetes

Diabetes can be prevented by certain lifestyle changes. We can easily prevent or delay the onset of type 2 diabetes by following ways.

- Maintain a healthy body weight as per body mass index.
- Regular physical exercise for 30 minutes daily.
- Avoid junk food, sugar and saturated fat. Eat a healthy diet.
- Quit smoking
- Manage stress and anxiety.
- Monitor and keep your blood pressure and cholesterol within normal range.
- Regular screening for diabetes.

Treatment of Diabetes

Managing diabetes is important to live a long and healthy life. Depending on type of diabetes, blood sugar monitoring, insulin and oral drugs may be taken for the treatment. Early treatment in people with prediabetes can also return their blood glucose levels to normal range.

1. Treatment for type 1 diabetes: Patients with type 1 diabetes are required to take insulin injections or insulin pump as a lifelong insulin therapy. Patients are advised to self-monitor their glucose level at home using glucose test strips. Depending on the glucose level, 2 or more injections of insulin may be advised by the doctor. Some of the patients may also be required to undergo pancreas transplant or islet cell transplant depending on the severity and on the recommendation of a doctor.
2. Treatment of type 2 diabetes: Oral anti diabetic drugs or insulin or both may be required to treat type 2 diabetes mellitus along with a healthy lifestyle, regular physical exercise and proper diet plan. Some of the oral antidiabetic drugs work by increasing the release of insulin by pancreas while some of them prevent the production and release of glucose by the liver. There are many different types of oral antidiabetic drugs having their own mechanism of action to reduce the blood sugar level. For example; metformin, glimepiride, sitagliptin, voglibose, dapagliflozin, etc.

Monitoring Diabetes At Home Using Glucometer

It is advised that patients with diabetes mellitus either type 1 or type 2 should monitor their blood glucose concentrations periodically at home using a glucometer. Glucometer is a simple device to measure the blood sugar level at home. Whenever the patient have the symptoms of hypoglycemia, this device is very helpful in such conditions. The patient can prick their finger with the needle provided with the device and a drop of blood is enough to measure the blood sugar level using this device [1-17].

Key Facts

- The number of people with diabetes increased from 108 million in 1980 to 422 million in 2014. Prevalence has been rising more rapidly in low and middle income countries than in high income countries.
- Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.
- Between 2000 and 2019, there was a 3% increase in diabetes mortality rates by age.
- In 2019, diabetes and kidney disease due to diabetes caused an estimated 2 million deaths.
- A healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use are ways to prevent or delay the onset of type 2 diabetes.
- Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication and regular screening and treatment for complications.

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