!! JAY AMBE !!

12. DIABETES

PREPARED BY

DR. NAITIK D. TRIVEDI,

M. PHARM, PH. D

LECTURER AT GOVERNMENT AIDED,

A. R. COLLEGE OF PHARMACY & G. H. PATEL INSTITUTE OF PHARMACY,

VALLABH VIDYANAGAR, ANAND, GUJARAT

Mobile: +91 - 9924567864

E-mail: mastermindnaitik@gmail.com

&

DR. UPAMA N. TRIVEDI,

M. PHARM, PH. D

ASSOCIATE PROFESSOR & HoD (Pharm. D),

INDUBHAI PATEL COLLEGE OF PHARMACY AND

RESEARCH CENTRE, DHARMAJ, GUJARAT

E-mail: ups.aasthu@gmail.com

12. DIABETES

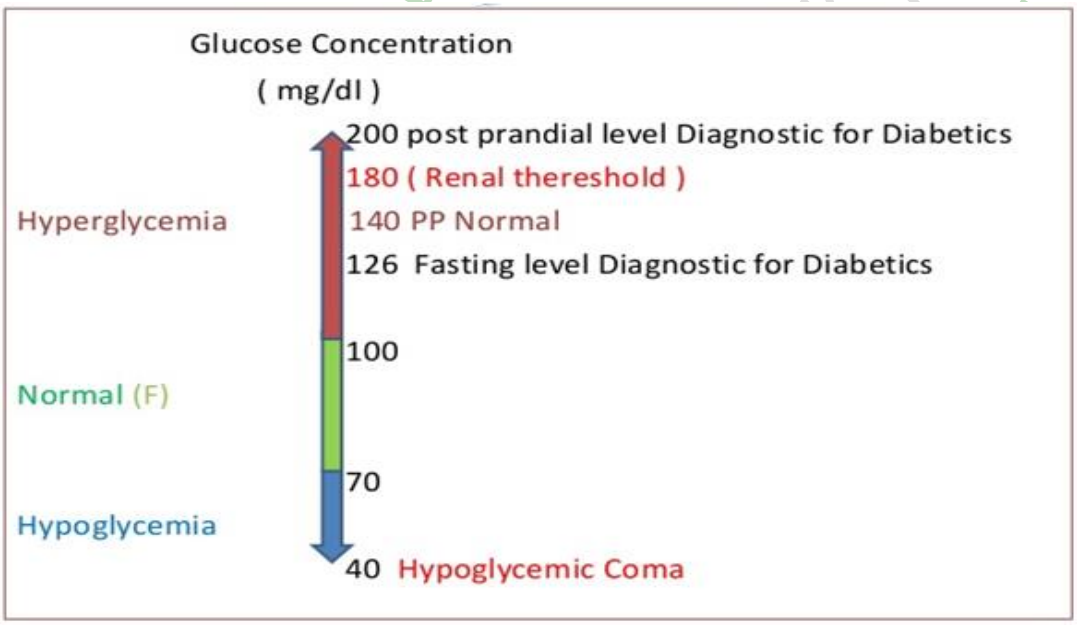
DEFINATION

Diabetes, often referred as diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (HYPERGLCEMIA), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both.

INTRODUCTION:

Patients with high blood sugar will typically experience:

- Polyuria (frequent urination),
- They will become increasingly thirsty (polydsypsia) and
- Hungry (polyphagia).



WHAT IS DIABETES?

- Diabetes (diabetes mellitus) is classed as a metabolism disorder. Metabolism refers to the way our bodies use digested food for energy and growth. Most of what we eat is broken down into glucose. Glucose is a form of sugar in the blood - it is the principal source of fuel for our bodies.
- However, glucose cannot enter our cells without insulin being present - insulin makes it possible for our cells to take in the glucose.

- Insulin is a hormone that is produced by the pancreas. After eating, the pancreas automatically releases an adequate quantity of insulin to move the glucose present in our blood into the cells, as soon as glucose enters the cells blood-glucose levels drop.
- A person with diabetes has a condition in which the quantity of glucose in the blood is too elevated (hyperglycemia). This is because the body does not produce enough insulin.
- High blood glucose levels are toxic, and cells that don't get glucose are lacking the fuel they need to function properly.

HOMEOSTASIS [REGULATION] OF GLUCOSE

- Homeostasis is the maintenance of a stable internal environment within an organism, and maintaining a stable internal environment in a human means having to carefully regulate many parameters, including glucose levels in the blood.

❖ **There are two major ways that signals are sent throughout the body.**

- The first is through nerves of the nervous system. Signals are sent as nerve impulses that travel through nerve cells, called neurons. These impulses are sent to other neurons, or specific target cells at a specific location of the body. This action is through adrenergic system.
- The second way that signals can be sent throughout the body is through the circulatory system. These signals are transmitted by specific molecules called hormones, which are signaling molecules that travel through the circulatory system. Glucose balance by pancreatic hormones. For e.g. insulin and glucagon

1. Sympathetic / Adrenergic system

➢ Stimulation of sympathetic system release adrenaline, a neurotransmitter/ metabolic hormone that helps mobilize energy stores in the form of glucose and free fatty acids in preparation for physical activity or for recovery from hypoglycemia by two ways.

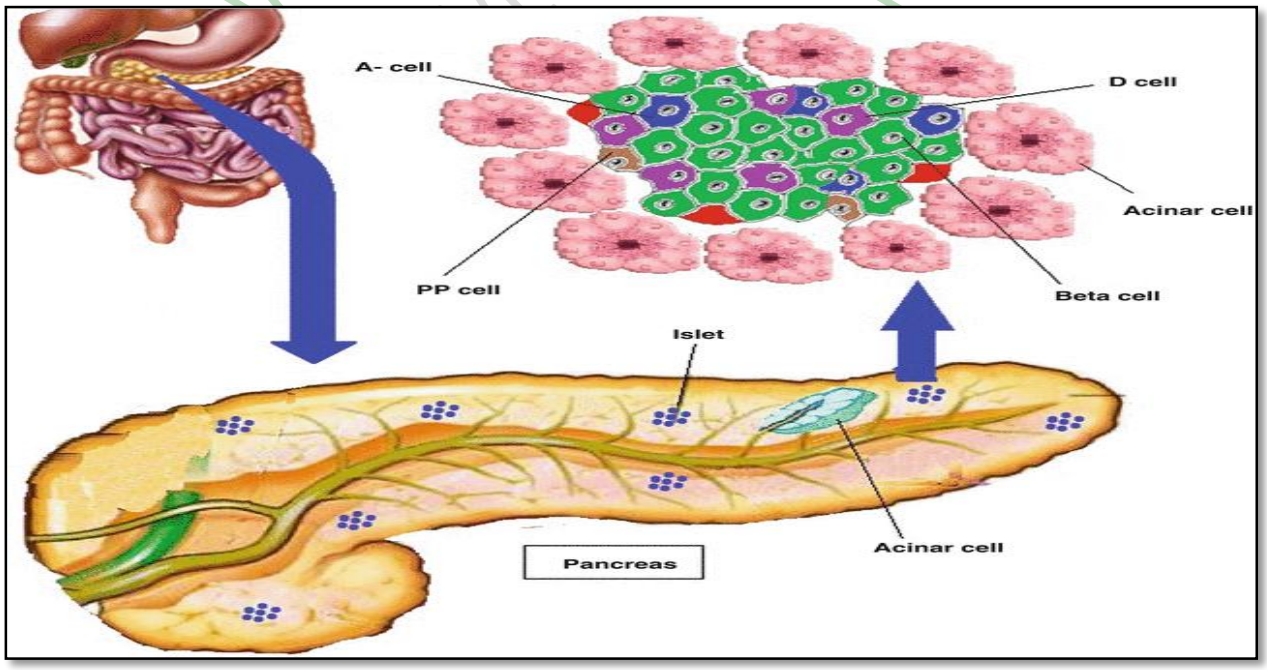
✓ Adrenaline increase blood glucose level by inhibiting secretion of insulin via alpha-2 receptor

✓ Adrenaline increase blood glucose level by increasing glycogenolysis in liver via beta-2 receptor

2. Pancreatic hormones

The **pancreas** is a long, slender organ, most of which is located posterior to the bottom half of the stomach. Although it is primarily an exocrine gland, secreting a variety of digestive enzymes, the pancreas has an endocrine function. Its **pancreatic islets**—clusters of cells formerly known as the islets of Langerhans—secrete the hormones glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).

SR.NO.	NAME OF CELL	NAME OF HORMONE	FUNCTION
1.	Alpha Cell	Glucagon	↓ BGL
2.	Beta Cell	Insulin	↑ BGL
3.	Delta Cell	Somatostatin	Regulate both alpha & beta cells secretions
4.	PP Cell	Pancreatic Polypeptide	Play a role in appetite, Regulation of pancreatic exocrine and endocrine secretions



PNACREAS

I] INSULIN

- Insulin is a polypeptide known as islet of amyloid peptide or amylin, with a molecular weight of about 6000 Daltons. It is composed of two chains, chain A and chain B both chains held together by disulfide bonds.

- **Insulin synthesis, store and release**

Insulin is synthesized in significant quantities only in beta cells in the pancreas.

↓

The insulin mRNA is translated as a single chain precursor called preproinsulin, and removal of its signal peptide during insertion into the endoplasmic reticulum generates proinsulin.

↓

Proinsulin consists of three domains: an amino-terminal B chain, a carboxy-terminal A chain and a connecting peptide in the middle known as the C peptide.

↓

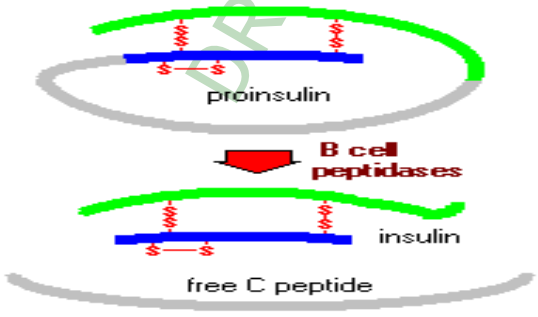
Within the endoplasmic reticulum, proinsulin is exposed to several specific endopeptidases which excise the C peptide, thereby generating the mature form of insulin.

↓

Insulin and free C peptide are packaged in the Golgi into secretory granules which accumulate in the cytoplasm.

↓

When the beta cell is appropriately stimulated, insulin is secreted from the cell by exocytosis and diffuses into islet capillary blood. C peptide is also secreted into blood, but has no known biological activity.



CONTROL OF INSULIN SECRETION

Insulin is secreted in primarily in response to elevated blood concentrations of glucose. This makes sense because insulin is "in charge" of facilitating glucose entry into cells. Some neural stimuli (e.g. sight and taste of food) and increased blood concentrations of other fuel molecules, including amino acids and fatty acids, also promote insulin secretion.

- The mature beta-granules form a large storage pool for insulin, well in excess of the daily requirement. Insulin is released into the circulation by fusion of the granules with the beta-cell membrane and exocytosis.
- A series of events triggers insulin secretion.
- Physiologically, glucose enters the beta-cell through an insulin independent process (probably involving the glucose transporter 1, GLUT-1).
- There it is phosphorylated by the enzyme glucokinase and metabolized through glycolysis and entry into the mitochondrial TCA cycle.
- This results in the generation of ATP which is transferred back to the cytosol and increases the ATP/ADP ratio.
- This increased ATP/ADP ratio leads to closure of the ATP-dependent potassium channel (K_{ATP} channel) which leads to depolarisation of the beta-cell membrane.
- The depolarisation of the cell membrane activates voltage-sensitive Ca^{2+} channels, leading to an influx of Ca^{2+} into the cell.
- This forms the final trigger for insulin exocytosis.
- The granule membrane is recycled to the Golgi apparatus following release of insulin.

GIT hormone also stimulate insulin secretions like:- gastric, secretin, cholecystokinin, gastric inhibitory peptide and glucagon like peptide (GLP & GLP1)

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I] INSULIN ACTIONS

Insulin and Carbohydrate Metabolism

- Glucose is liberated from dietary carbohydrate such as starch or sucrose by hydrolysis within the small intestine, and is then absorbed into the blood.
- Elevated concentrations of glucose in blood stimulate release of insulin, and insulin acts on cells throughout the body to stimulate uptake, utilization and storage of glucose.
- The effects of insulin on glucose metabolism vary depending on the target tissue.
- Two important effects are:

1. **Insulin facilitates entry of glucose into muscle, adipose and several other tissues.**

   The only mechanism by which cells can take up glucose is by facilitated diffusion through a family of hexose transporters.

   - ✓ In many tissues - muscle being a prime example - the major transporter used for uptake of glucose (called GLUT4) is made available in the plasma membrane through the action of insulin.
   - ✓ When insulin concentrations are low, GLUT4 glucose transporters are present in cytoplasmic vesicles, where they are useless for transporting glucose.
   - ✓ Binding of insulin to receptors on such cells leads rapidly to fusion of those vesicles with the plasma membrane and insertion of the glucose transporters, thereby giving the cell an ability to efficiently take up glucose.
   - ✓ When blood levels of insulin decrease and insulin receptors are no longer occupied, the glucose transporters are recycled back into the cytoplasm.S
   - ✓ Some tissues that do not require insulin for efficient uptake of glucose: important examples are brain and the liver. This is because these cells don't use GLUT4 for importing glucose, but rather, another transporter that is not insulin-dependent.

2. **Insulin stimulates the liver to store glucose in the form of glycogen.**

   - ✓ A large fraction of glucose absorbed from the small intestine is immediately taken up by hepatocytes, which convert it into the storage polymer glycogen.
   - ✓ Insulin has several effects in liver which stimulate glycogen synthesis.

Insulin and Lipid Metabolism

Insulin's also has important effects on lipid metabolism, including the following:

1. **Insulin promotes synthesis of fatty acids in the liver.**

- ✓ Insulin increased synthesis of fatty acids and TG in adipose tissues and liver
- ✓ Decreased lipolysis

2. Insulin inhibits breakdown of fat in adipose tissue

- ✓ By inhibiting the intracellular lipase that hydrolyzes triglycerides to release fatty acids.

MECHANISM OF INSULIN

Insulin is bind with specific receptor of target cell

↓

Receptor is large trancemembrane glycoprotein consisting 2-α & 2-β chain/ subunit

↓

A-subunit ie at extracellular and carries insulin binding side

↓

Whereas β-subunit is at intracellular with tr-pr-k [enzyme linked receptor]

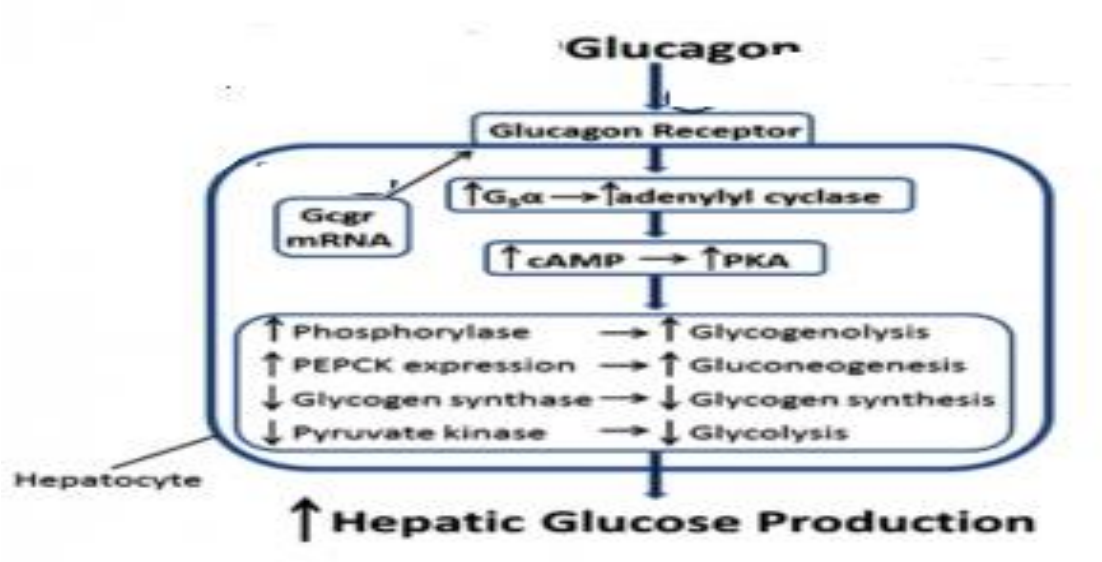
↓

Produce pharmacological action

II] GLUCAGON

- Glucagon -a single chain polypeptide of 29 amino acids- is a hormone that is produced by alpha cells in a part of the pancreas known as the islets of Langerhans & also synthesized by GIT.
- Both are structurally same
- GIT secretes – secretin & vaosactive intestinal peptide
- **Physiological stimuli of glucagon:-**
  - ✓ Amino acid [sp. Arginine]
  - ✓ High protein rich diet
  - ✓ Low conc. Plasma sugar
  - ✓ Adr- increased glucagon secretion through β- receptor

- **Mechanism of glucagon**



PEPCK- phosphoenol pyruvate carboxykinase

III] SOMATOSTATIN

- It is secreted by the D cells of the islets to inhibit the release of insulin and glucagon.
- It is also generated in the hypothalamus, where it inhibits the release of growth hormone and thyroid-stimulating hormones from the anterior
- **Synthesis**

- Somatostatin is initially secreted as a 116 amino acid precursor, preprosomatostatin,
- Which undergoes endoproteolytic cleavage to prosomastatin.
- Prosomastatin is further process into two active forms, somatostatin-14 (SST-14) and somatostatin-28 (SST-28)

➢ **The actions of somatostatin** are mediated via signaling pathways of G protein-coupled somatostatin receptors. Antineoplastic effects and potential uses of somatostatin on various tumours, including pituitary adenomas, GEP-NETs, paragangliomas, carcinoids, breast cancers, malignant lymphoma and small-cell lung cancers, have been extensively investigated [A20384]. Somatostatin has been used in the clinical setting for the diagnosis of acromegaly and gastrointestinal tract tumours.

IV] AMYLIN

Amylin is a peptide of 37 amino acids, which is also secreted by the beta cells of the pancreas.

Some of its actions:

- inhibits the secretion of glucagon;
- slows the emptying of the stomach;
- sends a satiety signal to the brain.

All of its actions tend to supplement those of insulin, reducing the level of glucose in the blood.

A synthetic, modified, form of amylin (pramlintide or Symlin®) is used in the treatment of type 2 diabetes.

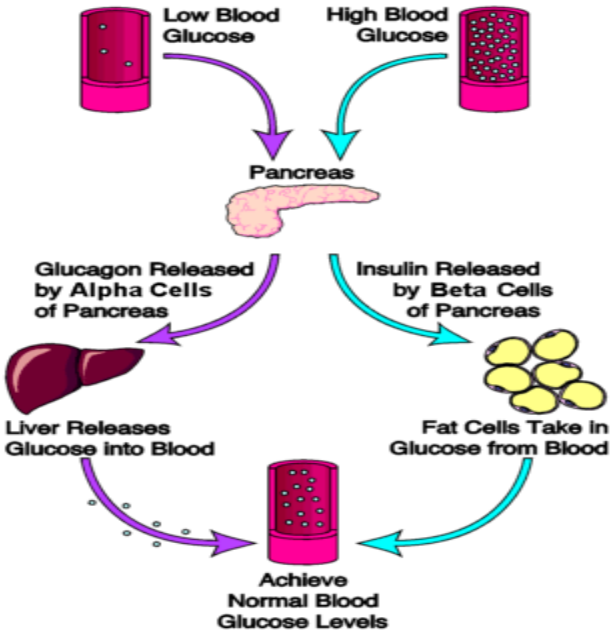
V] PP CELLS

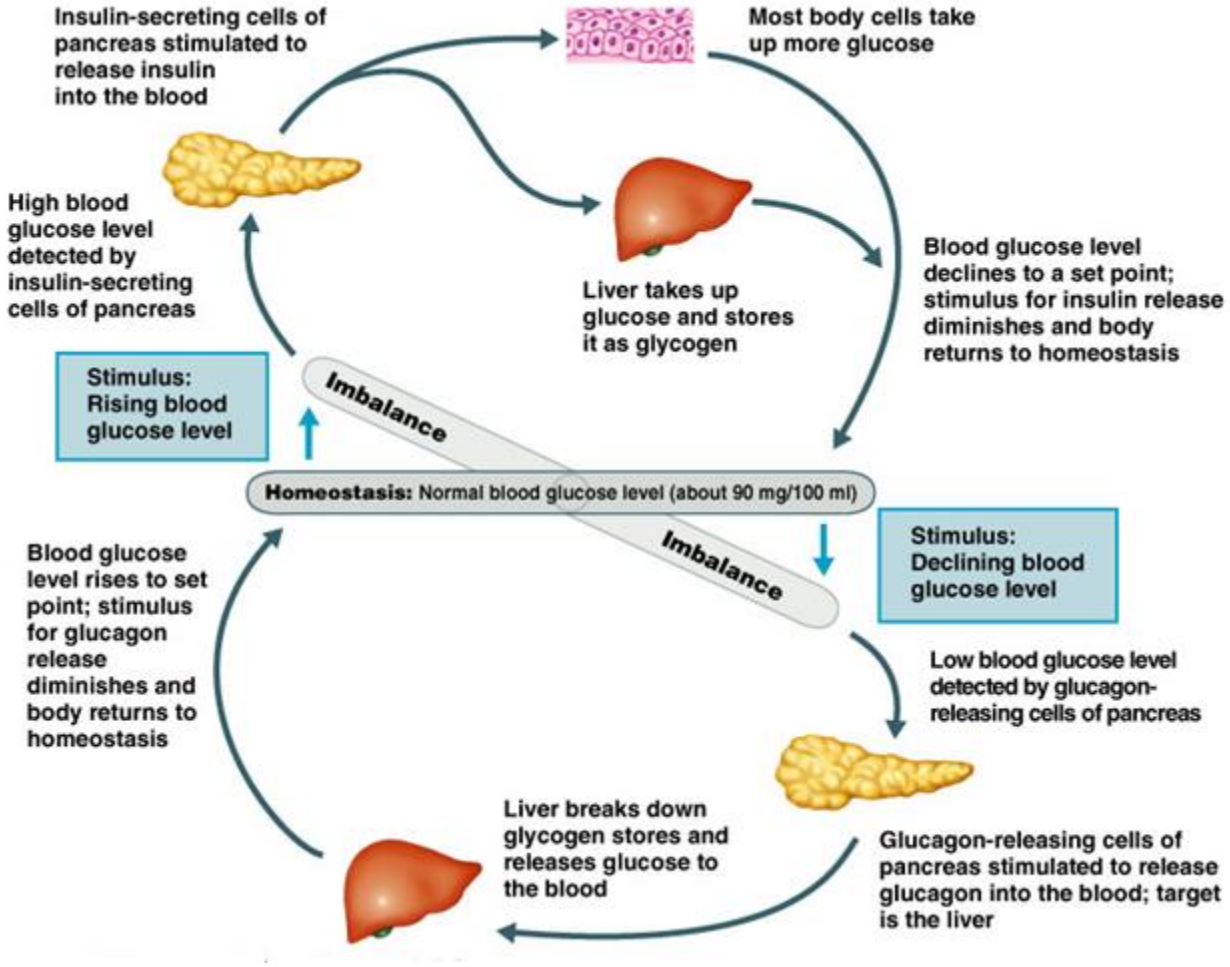
The PP cells of the islets secrete a 36-amino-acid **pancreatic polypeptide**, which reduces appetite.

VI] EPSILON CELLS

The epsilon cells of the islets secrete ghrelin, which stimulates appetite.

ROLE OF INSULIN AND GLUCAGON IN REGULATION OF GLUCOSE


Low Blood Glucose
High Blood Glucose
Pancreas
Glucagon Released by Alpha Cells of Pancreas
Insulin Released by Beta Cells of Pancreas
Liver Releases Glucose into Blood
Fat Cells Take In Glucose from Blood
Achieve Normal Blood Glucose Levels


Insulin-secreting cells of pancreas stimulated to release insulin into the blood
Most body cells take up more glucose
High blood glucose level detected by insulin-secreting cells of pancreas
Liver takes up glucose and stores it as glycogen
Blood glucose level declines to a set point; stimulus for insulin release diminishes and body returns to homeostasis
Stimulus: Rising blood glucose level
Imbalance
Homeostasis: Normal blood glucose level (about 90 mg/100 ml)
Imbalance
Stimulus: Declining blood glucose level
Blood glucose level rises to set point; stimulus for glucagon release diminishes and body returns to homeostasis
Low blood glucose level detected by glucagon-releasing cells of pancreas
Liver breaks down glycogen stores and releases glucose to the blood
Glucagon-releasing cells of pancreas stimulated to release glucagon into the blood; target is the liver

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TYPES OF DIABETES

1. **Type 1 Diabetes**
2. **Type 2 Diabetes**
3. **Gestational Diabetes**
4. **Prediabetes**

1. Type 1 Diabetes Mellitus:-Insulin Dependent Diabetes Mellitus [IDDM]

- Type 1 diabetes occurs when the pancreas cannot make insulin. Everyone with type 1 diabetes requires insulin injections. Most people are diagnosed with type 1 diabetes during their childhood or adolescent years.

2. Type 2 Diabetes Mellitus:-Non Insulin Dependent Diabetes Mellitus [NIDDM]

- Type 2 diabetes occurs when the pancreas does not make enough insulin or the body does not use insulin properly. It usually occurs in adults, although in some cases children may be affected. People with type 2 diabetes usually have a family history of this condition and 90% are overweight or obese. People with type 2 diabetes may eventually need insulin injections.

3. Gestational diabetes

- Another less common form is gestational diabetes, a temporary condition that occurs during pregnancy. Depending on risk factors, between 3% to 13% of women will develop gestational diabetes which can be harmful for the baby if not controlled. The problem usually clears up after delivery, but women who have had gestational diabetes have a higher risk of developing type 2 diabetes later in life.

4. Prediabetes

- Prediabetes is a term used to describe blood sugar levels that are higher than normal, but not high enough to be classified as diabetes. Many people with prediabetes go on to develop diabetes.

EPIDEMIOLOGY

- The incidence of type 1 diabetes is increasing worldwide, for unknown reasons. It is speculated that environmental changes may be causing modification to the diabetes-associated alleles.

- There are major ethnic and geographical differences in the prevalence and incidence of type 1 diabetes. Figures are highest in Caucasians (especially Scandinavians), while the disorder is rare in Japan and the Pacific area.
- In northern Europe, the prevalence is approximately 0.3% in those under 30 years of age. Type 1 diabetes may present at any age, but there is a sharp increase around the time of puberty and a decline thereafter. Approximately 50–60% of patients with type 1 will present before 20 years of age.
- Type 2 diabetes is much more common than type 1, accounting for 90% of people with diabetes. It usually occurs in those over the age of 40 years. Estimates in the UK suggest that type 2 diabetes currently affects approximately 2.3 million people, and up to another 500,000 are thought to be undiagnosed.
- The incidence of type 2 rises with age and with increasing obesity. As with type 1, there are major ethnic and geographical variations.
- India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken.
- The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease. Early identification of at-risk individuals using simple screening tools like the Indian Diabetes Risk Score (IDRS) and appropriate lifestyle intervention would greatly help in preventing or postponing the onset of diabetes and thus reducing the burden on the community and the nation as a whole.

ETIOLOGY

- **Type 1 diabetes**
  - Both genetic and environmental factors are relevant in the development of type 1 diabetes, but the exact relationship between the two is still unknown.

- Type 1 diabetes is believed to be an autoimmune condition. This means your immune system mistakenly attacks and destroys the beta cells in your pancreas that produce insulin. The damage is permanent.
- What prompts the attacks isn't clear. There may be both genetic and environmental reasons. Lifestyle factors aren't thought to play a role.
- There is a strong immunological component to type 1 and a clear association with many organ-specific autoimmune diseases. Circulating **islet cell antibodies** (ICAs) are present in more than 70% of those with type 1 at the time of diagnosis.
- Studies have been carried out in which patients with newly diagnosed type 1 were treated with immunosuppressive therapies such as ciclosporin, azathioprine, prednisolone and antithymocyte globulin.
- These therapies showed transient improvements in clinical measures and increased the rate of remissions in which insulin was not required. However, their use is limited in an otherwise healthy and young population due to potential toxicity and the risks associated with immune suppression.
- Studies have investigated the use of **anti-CD3 monoclonal antibodies**. When newly diagnosed type 1 patients are treated with short courses of anti-CD3 monoclonal antibodies, smaller insulin doses are required. This relates to better preservation of β-cell function.

➢ **Type 2 diabetes**

- Type 2 diabetes starts as insulin resistance. This means your body can't use insulin efficiently. That stimulates your pancreas to produce more insulin until it can no longer keep up with demand. Insulin production decreases, which leads to high blood sugar.
- Type 2 diabetes occurs because of the progressive development of insulin resistance and β-cell dysfunction, the latter leading to an inability of the pancreas to produce enough insulin to overcome the insulin resistance. About 85% of people with type 2 diabetes are obese.
- This highlights the clear association between type 2 and obesity, with obesity causing insulin resistance. In particular, central obesity, where adipose tissue is deposited intra-abdominally rather than subcutaneously, is associated with the highest risk. Body mass index (BMI) has been used as an indicator for predicting type 2 risk; however, it does not

take fat distribution into account, so waist circumference measurements are now being increasingly used.

- The exact cause of type 2 diabetes is unknown. Contributing factors may include:
  - ✓ genetics
  - ✓ lack of exercise
  - ✓ being overweight
  - ✓ There may also be other health factors and environmental reasons.

➢ **Gestational diabetes**

- Gestational diabetes is due to insulin-blocking hormones produced during pregnancy. This type of diabetes only occurs during pregnancy.

PATHOPHYSIOLOGY

TYPE 1 DIABETES MELLITUS

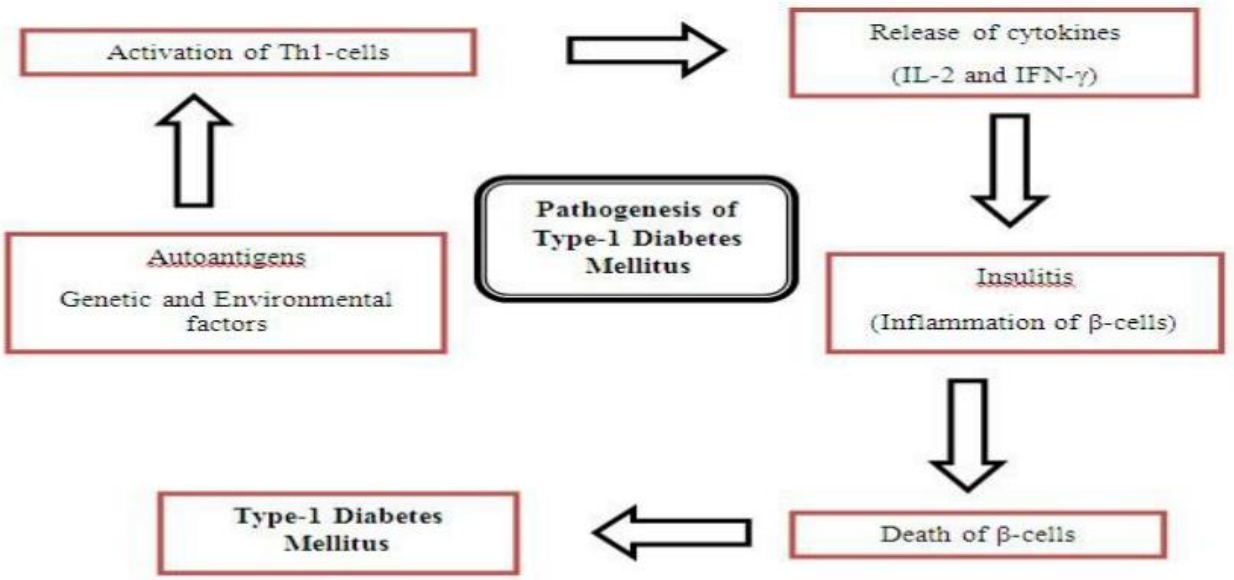
Type 1 Diabetes is characterized by autoimmune destruction of insulin producing cells in the pancreas by CD4+ and CD8+ T cells and macrophages infiltrating the islets. Several features characterize type 1 diabetes mellitus as an autoimmune disease :

1. Presence of immuno-competent and accessory cells in infiltrated pancreatic islets;
2. Association of susceptibility to disease with the class II (immune response) genes of the major histocompatibility complex (MHC; human leukocytes antigens HLA);
3. Presence of islet cell specific auto-antibodies;
4. Alterations of T cell mediated immune-regulation, in particular in CD4+ T cell compartment;
5. The involvement of monokines and TH1 cells producing interleukins in the disease process;
6. Response to immunotherapy and;
7. Frequent occurrence of other organ specific auto- immune diseases in affected individuals or in their family members.

❖ The autoimmune destruction of pancreatic β-cells, leads to a deficiency of insulin secretion which results in the metabolic derangements associated with T1DM.

❖ In addition to the loss of **insulin** secretion, the function of pancreatic α-cells is also abnormal and there is excessive secretion of glucagons in T1DM patients.

- Normally, hyperglycemia leads to reduced glucagons secretion, however, in patients with T1DM, glucagons secretion is not suppressed by hyperglycemia. The resultant inappropriately elevated glucagons levels exacerbate the metabolic defects due to insulin deficiency.
- This impairs glucose utilization and insulin deficiency also decreases the expression of a number of genes necessary for target tissues to respond normally to insulin such as glucokinase in liver and the GLUT 4 class of glucose transporters in adipose tissue explained that the major metabolic derangements, which result from insulin deficiency in T1DM are impaired glucose, lipid and protein metabolism.



Abbreviations: Th1, T helper cells; IL-2, Interleukin-2; IFN-γ, Interferon-gamma.

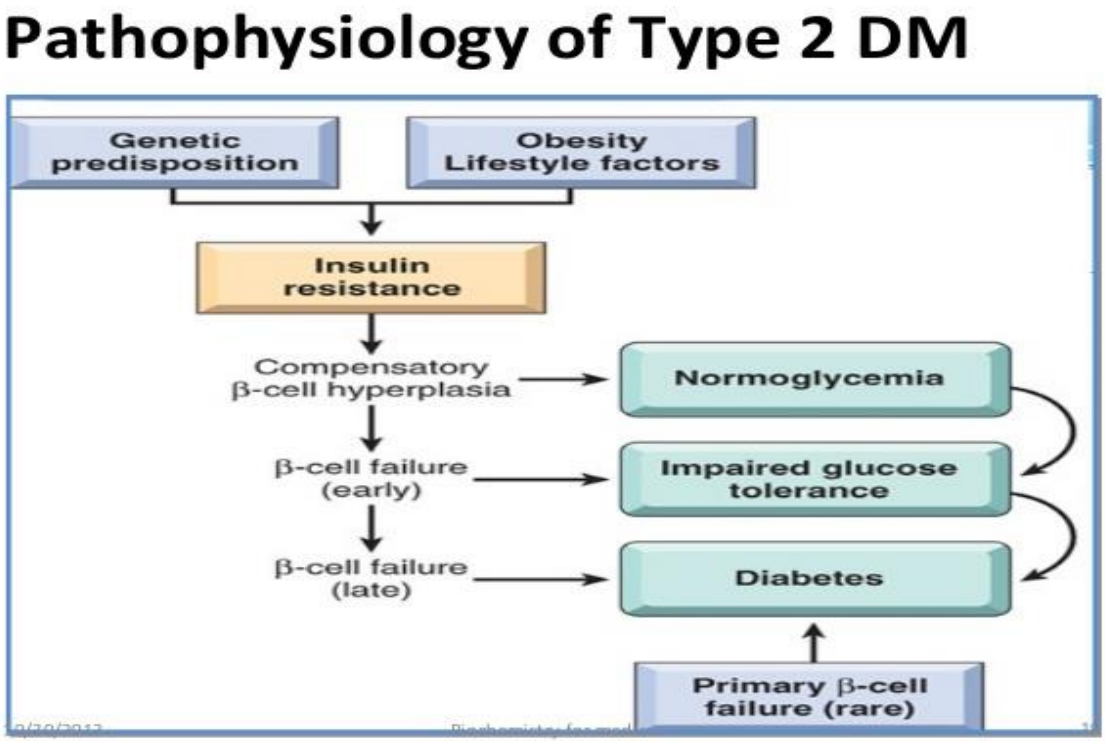
TYPE 2 DIABETES

- In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance
- In situations where resistance to insulin predominates, the mass of β-cells undergoes a transformation capable of increasing the insulin supply and compensating for the excessive and anomalous demand.
- The plasma insulin concentration (both fasting and meal stimulated) usually is increased, although "relative" to the severity of insulin resistance, the plasma insulin concentration is insufficient to maintain normal glucose homeostasis.

- Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance

Insulin resistance

- Abdominal fat, found in abundance in the majority of those with type 2 diabetes, is metabolically different from subcutaneous fat and can cause 'lipotoxicity'.
- Abdominal fat is resistant to the antilipolytic effects of insulin, resulting in the release of excessive amounts of free fatty acids, which in turn lead to insulin resistance in the liver and muscle.
- The effect is an increase in gluconeogenesis in the liver and an inhibition of insulin-mediated glucose uptake in the muscle.
- Both these result in increased levels of circulating glucose.
- Further, excess fat itself may contribute to insulin resistance because when adipocytes become too large they are unable to store additional fat, resulting in fat storage in the muscles, liver and pancreas, causing insulin resistance in these organs.



RISK FACTORS

Type 1 diabetes

- The chance of developing type 1 diabetes is increased if a parent or sibling also has diabetes.
- In type 1 diabetes, the body makes no or very little insulin. It affects around 5 percent of those with diabetes. It is treated with either insulin injections or an insulin pump, along with diet.
- The main risk factors for type 1 diabetes include:
  - ✓ **Family history**. Having a parent or sibling with type 1 diabetes increases the chances of a person having the same type. If both parents have type 1, the risk is even higher.
  - ✓ **Age**. Type 1 diabetes usually affects younger people. Ages 4 to 7 and ages 10 to 14 are the most common. Type 1 diabetes may occur at other ages, although it does so less often.
  - ✓ **Genetics**. Having certain genes may increase the risk of type 1 diabetes. Your doctor can check for these genes.
  - ✓ **Where a person lives**. Studies have found more type 1 diabetes the further away from the equator a person lives.

Type 2 diabetes

- Type 2 diabetes is the most common kind of diabetes.
- The body can still make some insulin, but is not able to use it the way it should. This leads to a buildup of sugar in the blood, which results in damage to the body.
- Unlike type 1, it is often treated with medicines taken by mouth. However, insulin injections may still be necessary if type 2 diabetes is uncontrolled.
- Type 2 diabetes has two kinds of risk factors. One kind of risk factor cannot be avoided. The other kind of risk factor, however, can be avoided.
- **Unavoidable risk factors**
  - ✓ family history
  - ✓ having a baby weighing more than 9 pounds
  - ✓ race
  - ✓ age
  - ✓ dark, thick, velvety skin appearing around the neck or armpits
  - ✓ history of gestational diabetes

- **Risk factors that can be avoided or treated**

  Risk factors for type 2 diabetes that can be avoided include getting no exercise and being overweight or obese.

  - ✓ obesity or being overweight, especially around the waist
  - ✓ getting little or no exercise
  - ✓ high blood pressure
  - ✓ heart or blood vessel disease and stroke
  - ✓ low levels of "good" cholesterol (HDL)., high levels of fats, called triglycerides
  - ✓ certain mental health conditions, stress
  - ✓ polycystic ovary syndrome
  - ✓ smoking
  - ✓ too much or too little sleep

Gestational diabetes

- Gestational diabetes is diabetes during pregnancy. Most women who are affected have not had diabetes before, and it goes away after the baby is born.
- However, once a woman has had gestational diabetes, the chances are that it will return in future pregnancies.
- Risk factors for gestational diabetes are much the same as other kinds of diabetes. These include:
  - ✓ being over 25 years of age
  - ✓ family or personal history of diabetes
  - ✓ prediabetes, which is high blood glucose without diabetes
  - ✓ unexplained stillbirth in the past
  - ✓ being overweight or obese
  - ✓ unhealthful eating
  - ✓ race

SIGN AND SYMPTOMS

1. **Frequent urination**
   - ✓ Excessive thirst and frequent urination are classic symptoms of diabetes.
   - ✓ If insulin is ineffective, or not there at all, kidneys cannot filter the glucose back it into the blood. The kidneys will take water from blood in order to dilute the glucose - which in turn fills up your bladder.
2. **Disproportionate thirst**
   - ✓ If you are urinating more than usual, you will need to replace that lost liquid. You will be drinking more than usual.
3. **Intense hunger**
   - ✓ As the insulin in our blood is not working properly, or is not there at all, and our cells are not getting their energy, your body may react by trying to find more energy - food. We will become hungry.
4. **Weight gain**
   - ✓ This might be the result of the above symptom (intense hunger).
5. **Unusual weight loss**
   - ✓ This is more common among people with Diabetes Type 1. As our body is not making insulin it will seek out another energy source. Muscle tissue and fat will be broken down for energy. As Type 1 is of a more sudden onset and Type 2 is much more gradual, weight loss is more noticeable with Type 1.
6. **Increased fatigue**
   - ✓ If our insulin is not working properly, or is not there at all, glucose will not be entering our cells and providing them with energy. This will make feel tired and listless.
7. **Irritability**
   - ✓ Irritability can be due to lack of energy.
8. **Blurred vision**
   - ✓ This can be caused by tissue being pulled from eye lenses. This affects eyes' ability to focus. With proper treatment this can be treated. There are severe cases where blindness or prolonged vision problems can occur.

9. Cuts and bruises don't heal properly or quickly

- ✓ Cuts and bruises take a much longer time than usual to heal. When there is more sugar (glucose) in your body, its ability to heal can be undermined.

10. More skin and/or yeast infections

- ✓ When there is more sugar in body, its ability to recover from infections is affected. Women with diabetes find it especially difficult to recover from bladder and vaginal infections.

11. Itchy skin

- ✓ A feeling of itchiness on your skin is sometimes a symptom of diabetes.

12. Gums are red and/or swollen - Gums pull away from teeth

- ✓ If gums are tender, red and/or swollen this could be a sign of diabetes. Your teeth could become loose as the gums pull away from them.

13. Frequent gum disease/infection

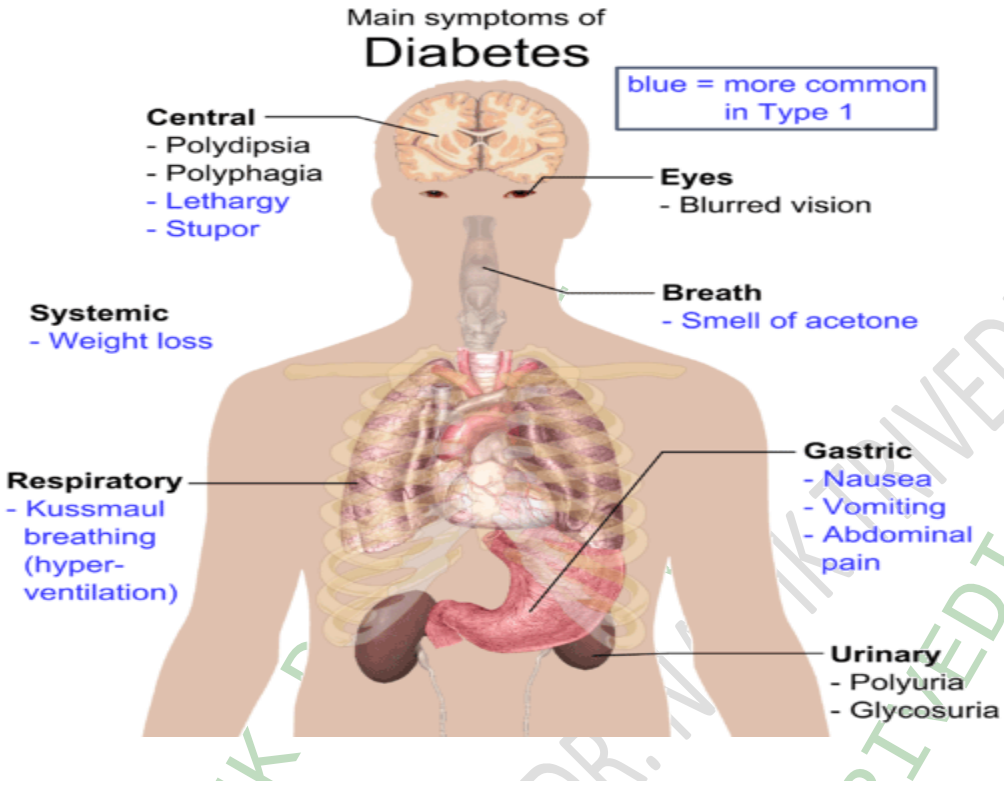
- ✓ As well as the previous gum symptoms, you may experience more frequent gum disease and/or gum infections.

14. Sexual dysfunction among men

- ✓ If you are over 50 and experience frequent or constant sexual dysfunction (erectile dysfunction), it could be a symptom of diabetes.

15. Numbness or tingling, especially in your feet and hands

- ✓ If there is too much sugar in body nerves could become damaged, as could the tiny blood vessels that feed those nerves.



Diagnosis	A1C (percent)	Fasting plasma glucose (FPG)[a]	Oral glucose tolerance test (OGTT)[ab]	Random plasma glucose test (RPG)[a]
Normal	below 5.7	99 or below	139 or below	
Prediabetes	5.7 to 6.4	100 to 125	140 to 199	
Diabetes	6.5 or above	126 or above	200 or above	200 or above

DIABETIC EMERGENCIES

HYPOGLYCEMIA

- Hypoglycemia, also called low blood glucose or low blood sugar, occurs when the level of glucose in blood drops below normal. For many people with diabetes, that means a level of 70 milligrams per deciliter (mg/dL) or less.
- Hypoglycemia can be a side effect of insulin or other types of diabetes medicines that help your body make more insulin. Two types of diabetes pills can cause hypoglycemia: sulfonylureas and meglitinides.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is a life-threatening problem that affects people with diabetes. It occurs when the body starts breaking down fat at a rate that is much too fast. The liver processes the fat into a fuel called ketones, which causes the blood to become acidic.

The fat is broken down by the liver into a fuel called ketones.

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Ketones are normally produced when the body breaks down fat after a long time between meals.

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When ketones are produced too quickly and build up in the blood and urine, they can be toxic by

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making the blood acidic.

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This condition is known as ketoacidosis.

LONG-TERM DIABETIC COMPLICATIONS

Complications of diabetes generally develop over time. Having poorly controlled blood sugar levels increases the risk of serious complications that can become life-threatening. Chronic complications include:

1. Macrovascular complications:
    - Cardiovascular diseases
    - Peripheral vascular diseases:- vessel disease, leading to heart attack or stroke
2. Microvascular complications
    - eye problems, called retinopathy
    - nerve damage, or neuropathy
    - kidney damage, or nephropathy

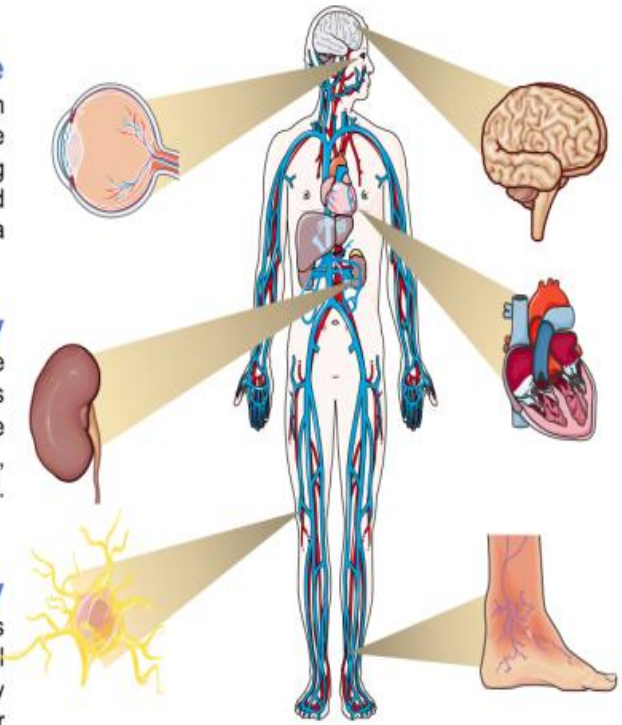
Major Complications of Diabetes

Microvascular

Eye
High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

Kidney
High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

Neuropathy
Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.



Macrovascular

Brain
Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

Heart
High blood pressure and insulin resistance increase risk of coronary heart disease

Extremities
Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.