Al-Mustaqbal University College

Pathophysiology 3rd stage

Diabetes Mellitus

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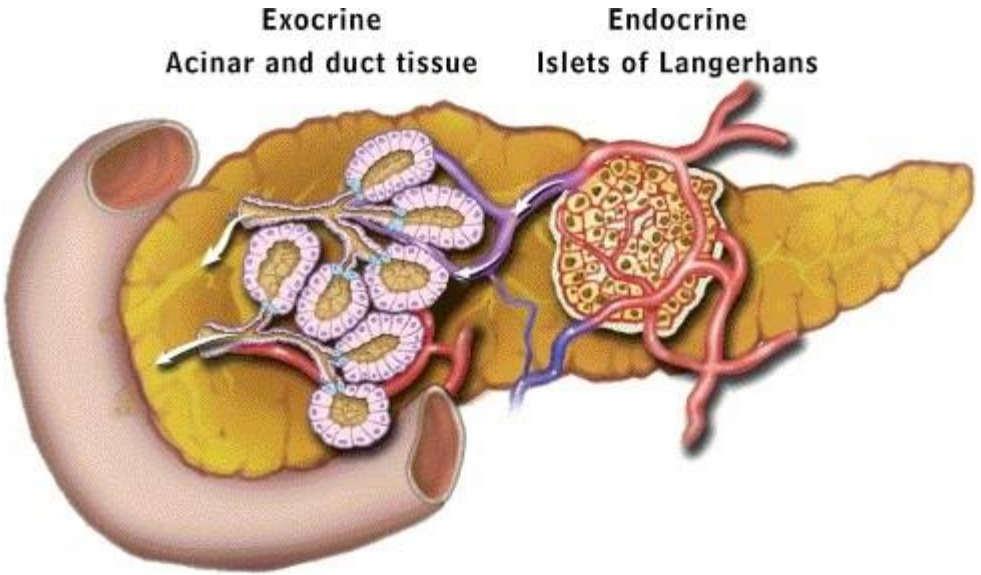
The Pancreas and Diabetes Mellitus (DM)

The pancreas is a large, diffuse abdominal organ that functions as both an exocrine and endocrine gland.

Physiologic Concepts

Exocrine Functions of the Pancreas

The exocrine functions of the pancreas involve the synthesis and release of digestive enzymes and sodium bicarbonate from specialized cells of the pancreas called acini cells.



Secretion of Pancreatic Enzymes

The pancreatic enzymes are secreted as inactive proenzymes that are activated when they reach the duodenum.

The activated enzymes include trypsin, amylase, and lipase, which are responsible for the digestion of proteins to amino acids, carbohydrates to simple sugars, and fats to free fatty acids and monoglycerides, respectively.

Secretion of Sodium Bicarbonate

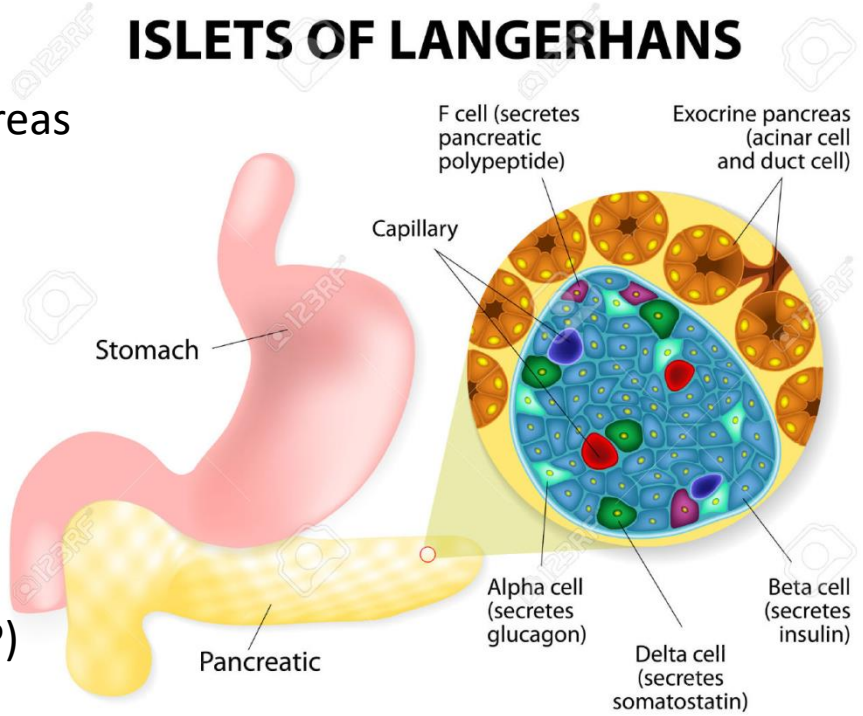
Sodium bicarbonate is secreted from pancreatic ductal cells in response to a second small-intestine hormone, secretin. to neutralizes acidic chyme which come from stomach.

Endocrine Functions of the Pancreas

The endocrine functions of the pancreas involve the synthesis and release of the hormones insulin, glucagon, and somatostatin.

Islets of langerhans

- Clusters of cells between acini of exocrine pancreas
- 150 µm diameter
- Consist of four types of cells:
- A or α cells (20%) secrete glucagon
- B or β cells (75%) secrete insulin
- D or γ cells (3-5%) secrete somatostatin
- F or δ (< 2%) secrete pancreatic polypeptide (PP)



Insulin

Control blood glucose level, storage and utilization of glucose.

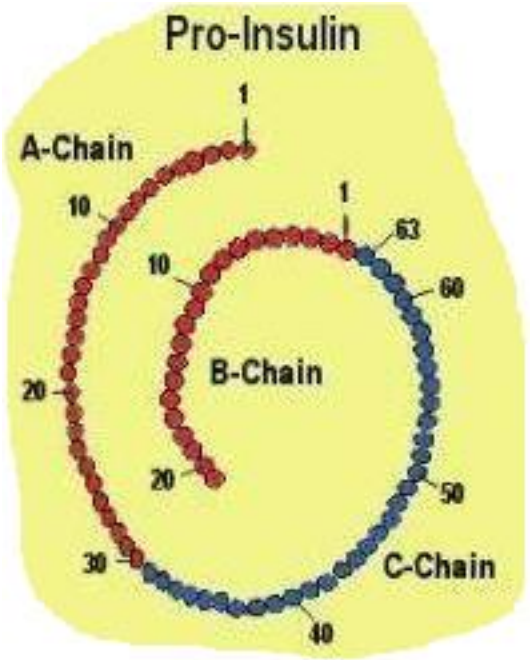
5 min half life.

Is a polypeptide (51 amino acids) consist of tow chains connecting together by disulphide bridges.

A chain (21 amino acids).

B chain (30 amino acids).

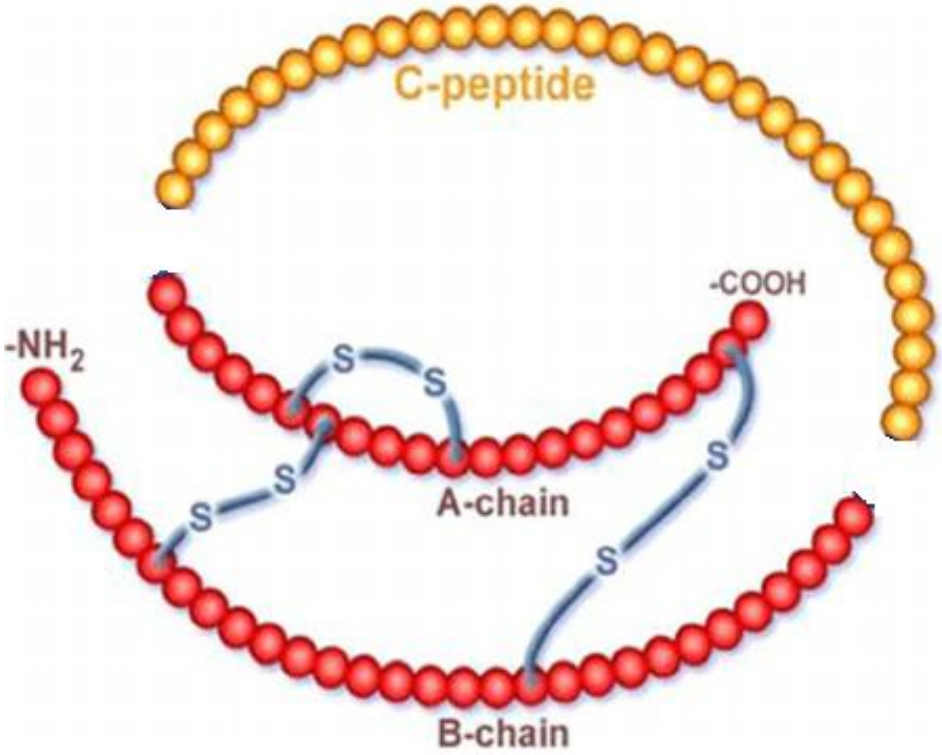
Proinsulin consist of C chain removed before insulin secretion.



Synthesis and Secretion of Insulin

The synthesis of insulin in the pancreas comes from the enzymatic cleavage of the molecule proinsulin.

Enzymatic cleavage of the C peptide connections leaves the A and the B peptides connected to each other through only the two disulfide bonds.

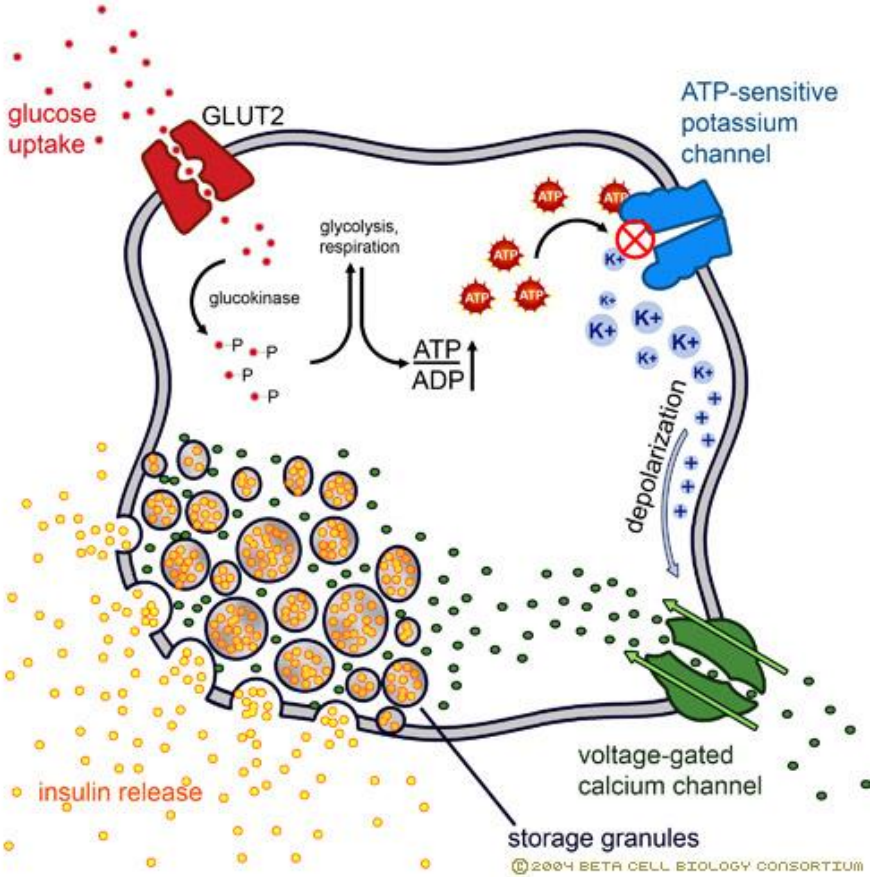


Insulin is released at a basal rate by the beta cells of the islets of Langerhans.

A rise in blood glucose is the **primary stimulus** to increase insulin release above baseline.

Fasting blood glucose level is normally 80 to 90 mg/100 mL of blood.

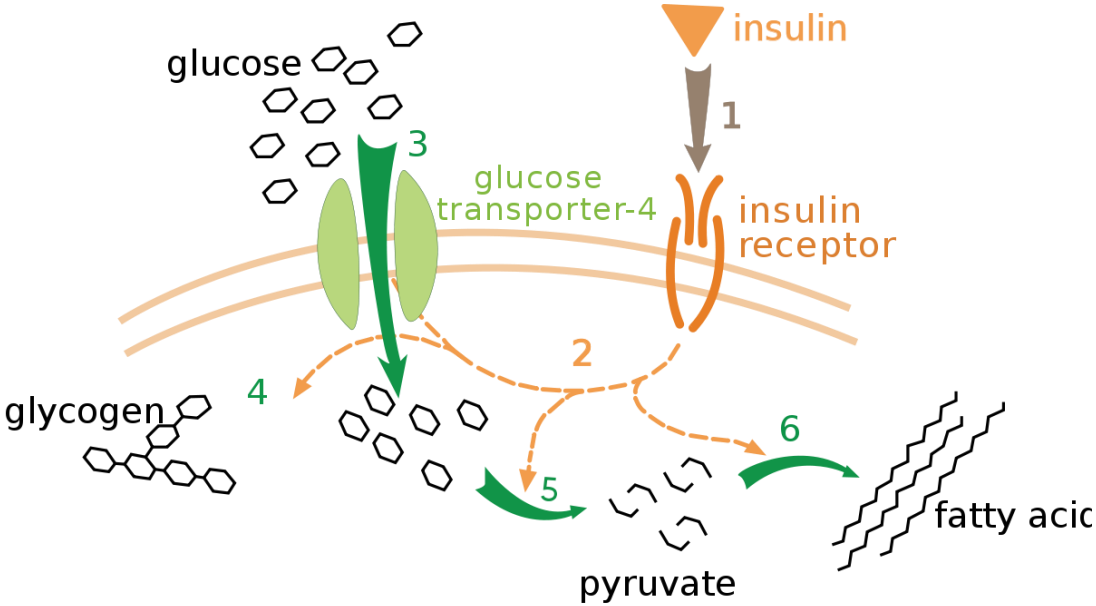
When blood glucose increases to more than 100 mg/100 mL of blood, insulin secretion from the pancreas increases rapidly and then returns to baseline in 2 to 3 hours.



Insulin activates glucose-transporter molecules, called glut-4 glucose transporters, which necessary for the facilitated diffusion of glucose into most cells.

inside the cells, glucose can be used for immediate energy production through the Krebs cycle or it can be stored in the cell as glycogen.

When glucose is carried into the cell, it results in decreased blood levels of glucose, reducing further stimulation of insulin release.



Insulin release is also regulated by:

2- Amino acids and the hormones of digestion cholecystokinin (CCK), secretin, and glucose-dependent insulinotropic polypeptide [GIP].

3- Parasympathetic nerves to the pancreas.

Both the release of GIP and the activation of the autonomic nervous system occur when one starts eating, resulting in a release of insulin at the beginning of a meal, even before glucose is absorbed.

While Sympathetic stimulation to the pancreas decreases insulin release via α receptors.

4- High level of ketoacids stimulate insulin secretion.

5- Somatostatin inhibit secretion of insulin.

6- Thiazide diuretics inhibit it secretion.

Insulin action:

1- Stimulating glucose uptake by cells and maintain plasma glucose levels.

2- Increases amino acid transport into cells and stimulates protein synthesis.

3- Inhibits the breakdown of fat, protein, and glycogen stores.

4- Inhibits gluconeogenesis.

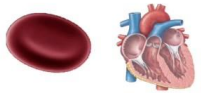
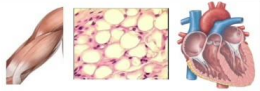
5- Increase K^+ up take by increasing Na^+-K^+ pump.

The Brain, Glucose, and Insulin

Unlike most other cells, brain cells do not require insulin for glucose entry.

Also unlike other cells that may use free fatty acids or amino acids for energy, brain cells must use only glucose or glycogen to meet their energy demands and drive their cellular functions.

In other words, brain cells are obligate users of glucose and glycogen. This means that gluconeogenesis by the liver is important;

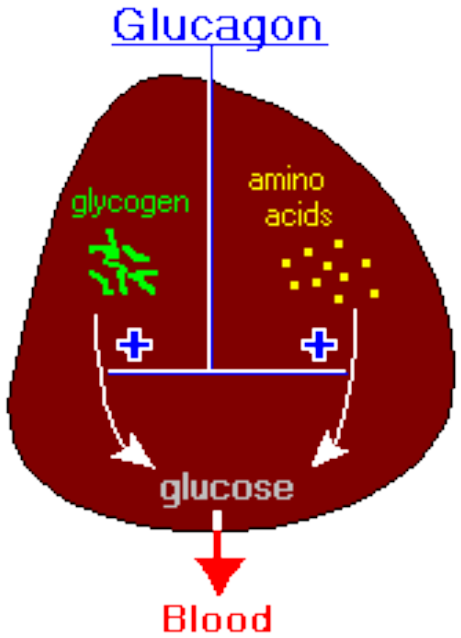
GLUT1	• Blood • Blood-Brain Barrier • Heart (lesser extent) 	• Insulin-Independent
GLUT2	• Liver • Pancreas • Small Intestine 	• Insulin-Independent • High K_m • Low Affinity
GLUT3	• Brain • Neurons • Sperm 	• Insulin-Independent • Low K_m • High Affinity
GLUT4	• Skeletal Muscle • Adipose Tissue • Heart 	
GLUT5		

Secretion of Glucagon

Glucagon is a protein hormone released from the alpha cells of the islets of Langerhans in response to low blood glucose levels and increased plasma amino acids.

Glucagon is primarily a hormone of the postabsorptive stage of digestion that occurs during fasting periods in between meals.

Its functions are mainly catabolic (breaking down).



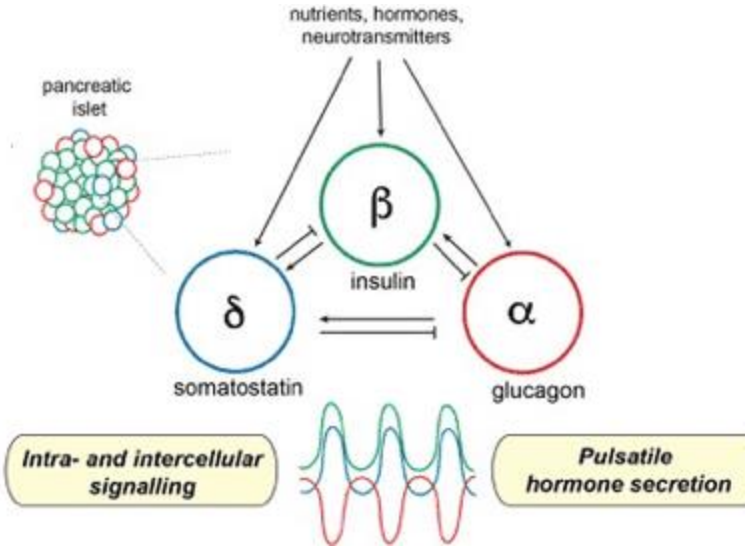
Secretion of Somatostatin

Secreted by **delta** cells.

Called **“growth hormone inhibiting hormone”** and is released as well by the hypothalamus.

Somatostatin from the hypothalamus inhibits the release of growth hormone from the anterior pituitary.

Somatostatin releasing from the pancreas to control metabolism by inhibiting the secretion of **insulin and glucagon**.



Diabetes mellitus (DM)

DM is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

Diabetes mellitus is derived from the Greek word **diabetes** meaning siphon - to pass through and the Latin word **mellitus** meaning honeyed or sweet.

Hyperglycemia
Hyperglycemia is defined as plasma glucose higher than the normal, fasting range of 126 mg/100 mL of blood.

Hyperglycemia is caused by:

1- Insulin deficiency, as seen in type 1 diabetes.

2- Decreased cellular responsiveness to insulin, as seen in type 2 diabetes.

3- Cushing's syndrome can cause hyperglycemia by stimulation of liver gluconeogenesis.

4- Prolonged high levels of thyroid hormone, prolactin, and growth hormone overstimulate insulin release by beta cells of the pancreas, leading to an eventual decrease in the cellular response to insulin.

5- The catecholamines epinephrine and norepinephrine inhibit insulin secretion, increase the breakdown of stored fats, and promote the use of glycogen for energy.

The American Diabetes Association (ADA) classifies four categories of diabetes mellitus, as follows:

1. Type 1 (beta-cell destruction, usually leading to absolute insulin deficiency).

2. Type 2 (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance).

3. Other specific types.

4. Gestational diabetes.

Type 1 Diabetes Mellitus

Type 1 diabetes is most commonly seen in non-obese individuals less than 30 years old and occurs in a slightly higher proportion of males than females. It is autoimmune antibody directed against B cells.

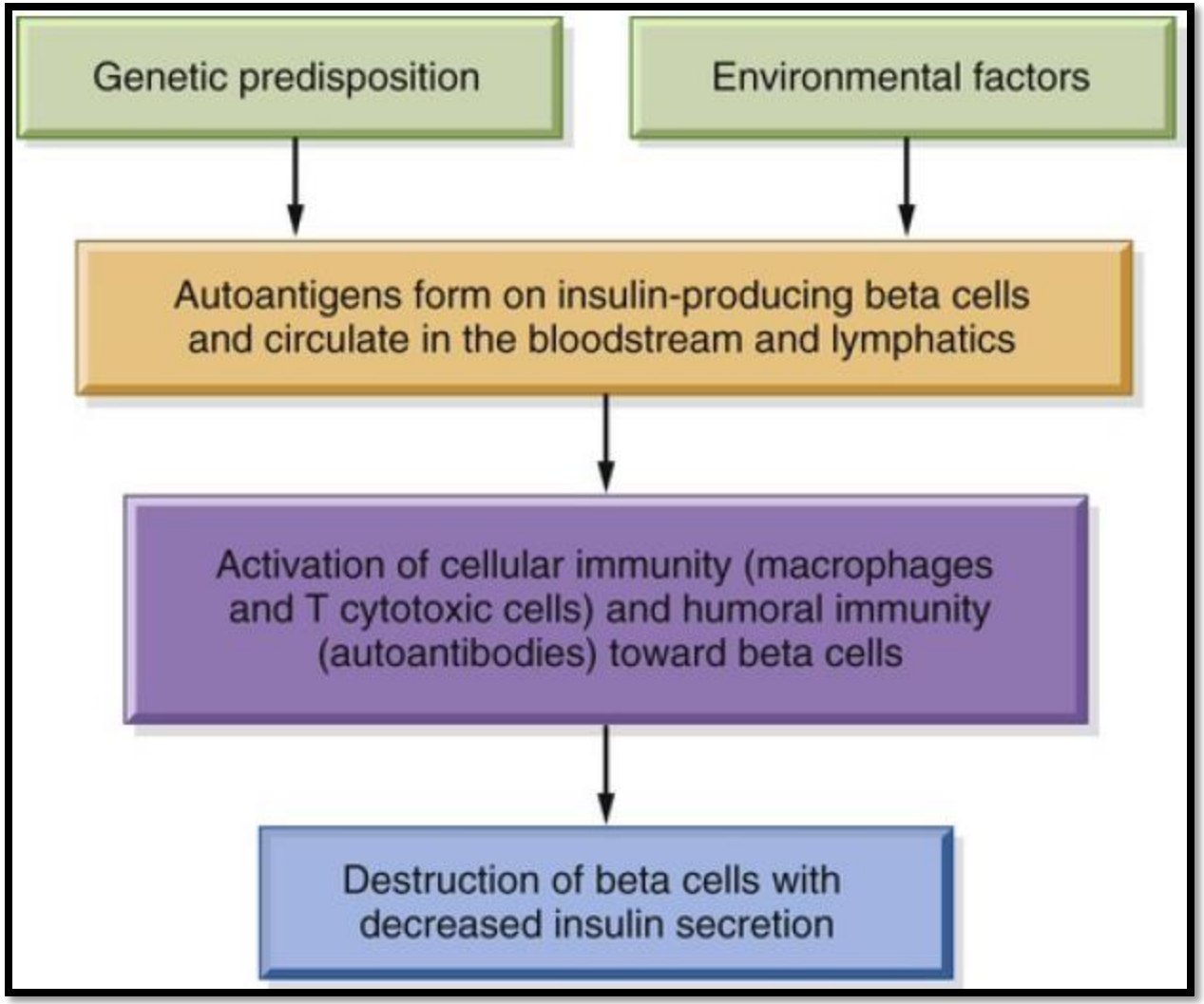
Autoimmune type 1 diabetes mellitus is a slowly progressive autoimmune T-cell–mediated disease that destroys beta cells of the pancreas.

Destruction of beta cells is related to genetic susceptibility and environmental factors.

Environmental factors that have been implicated include exposure to certain drugs, foods, and viruses.

These gene-environment interactions result in the formation of autoantigens that are expressed on the surface of pancreatic beta cells and circulate in the bloodstream and lymphatics.

Pathophysiology of Type 1 Diabetes Mellitus



Characteristics of type 1 diabetes

type 1 diabetes usually develops slowly over the course of many years, with the presence of autoantibodies against the beta cells and their steady destruction occurring well in advance of diagnosis.

By the time type 1 diabetes is diagnosed, there is usually little or no insulin being secreted from the pancreas, and more than 80% of the pancreatic beta cells have been destroyed.

The catabolic action of glucagon is unopposed by insulin and cells switch to the use of free fatty acids for energy.

Clinical Manifestations and Mechanisms for Type 1 Diabetes Mellitus

1- Polydipsia : Because of elevated blood glucose levels, water is osmotically attracted from body cells, resulting in intracellular dehydration and stimulation of thirst in hypothalamus.

2- Polyuria: Hyperglycemia acts as an osmotic diuretic.

3- Polyphagia: Depletion of cellular stores increase in hunger.

4- Weight loss: Because of fluid loss in osmotic diuresis and loss of body tissue as fats and proteins are used for energy.

5- Fatigue: Poor use of food products, contributing to lethargy and fatigue.

6- Recurrent infections: Growth of microorganisms is stimulated by increased glucose levels.

7- **Prolonged wound healing**: Impaired blood supply hinders healing.

8- **Genital pruritus:** Hyperglycemia and glycosuria favor fungal growth; candidal infections, resulting in pruritus, are a common presenting symptom in women.

9- **Blurred vision:** occurs as water balance in eye fluctuates because of elevated blood glucose levels; diabetic retinopathy may ensue

10- **Paresthesias:** Paresthesias are common manifestations of diabetic neuropathies.

11- Some individuals with type 1 diabetes are obese and may have manifestations of metabolic syndrome, including dyslipidemia, and hypertension.

12- **Nausea** or vomiting: due to dehydration and Ketones production.

Diagnostic Criteria for Diabetes Mellitus

In most cases, the suspicion of type 1 diabetes arises clearly with a history of polyuria, polydipsia, polyphagia, and weight loss. The individual may experience repeated vomiting and appear very sick.

1. HbA1C (hemoglobin A1C or glycosylated hemoglobin) ≥6.5%

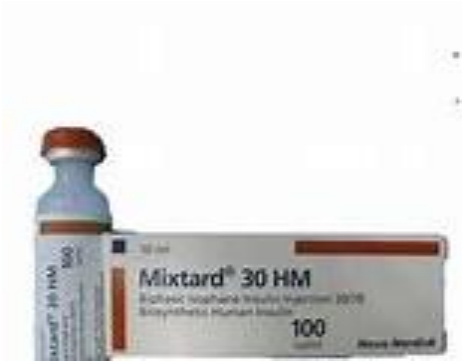
OR 2. fasting plasma glucose ≥126 mg/dl (7.0 mmol/L); fasting is defined as no caloric intake for at least 8 hr.

OR 3. 2-hr plasma glucose ≥200 mg/dl (11.1 mmol/L) during oral glucose tolerance testing.

OR 4. In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/L)

Patient with classical symptoms and single reading > 200 or $HbA_{1c} \geq 6.5$ consider as DM .

Management requires individual planning according to type of disease, age, and activity level, but all individuals require some combination of insulin therapy, meal planning, and exercise regimen.



Type 2 Diabetes Mellitus

Hyperglycemia caused by cellular insensitivity to insulin is called type 2 diabetes mellitus.

In type 2 diabetes mellitus, women are over-represented compared with men.

The most well-recognized risk factors a

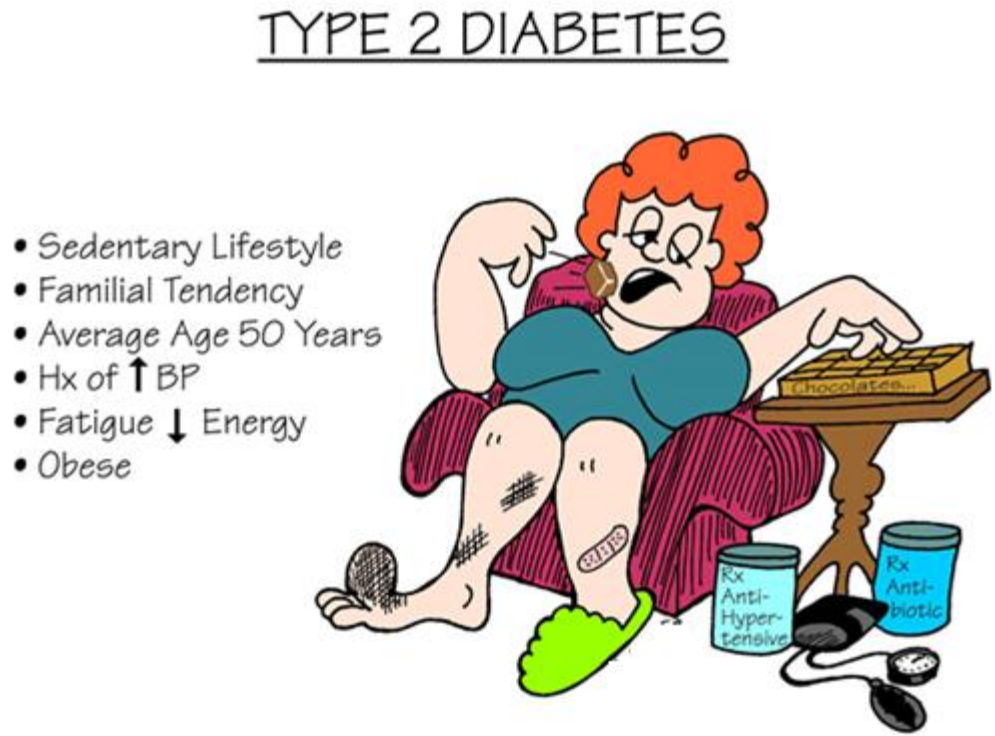
age,

obesity,

hypertension,

physical inactivity,

and family history.



Causes of type 2 diabetes

For most individuals, the number one risk factor for type 2 diabetes mellitus is obesity.

In addition, the genetic tendency to develop the disease is strong.

A genetic-environmental interaction appears to be responsible for type 2 diabetes.

Pathophysiology

Many organs contribute to insulin resistance, chronic hyperglycemia, and the consequences of type 2 diabetes.

Insulin resistance is defined as a suboptimal response of insulin-sensitive tissues (especially liver, muscle, and adipose tissue) to insulin and is associated with obesity.

Several mechanisms are involved in abnormalities of the insulin signaling pathway and contribute to insulin resistance.

These include:

- An abnormality of the insulin molecule,
- High amounts of insulin antagonists,
- Down-regulation of the insulin receptor,
- Alteration of glucose transporter (GLUT) proteins.

Obesity is one of the most important contributors to insulin resistance and diabetes and acts through several **important mechanisms**:

1. Adipokines (leptin and adiponectin) are hormones produced in adipose tissue. Obesity results in increased serum levels of leptin and decreased levels of adiponectin. These changes are associated with inflammation and decreased insulin sensitivity.

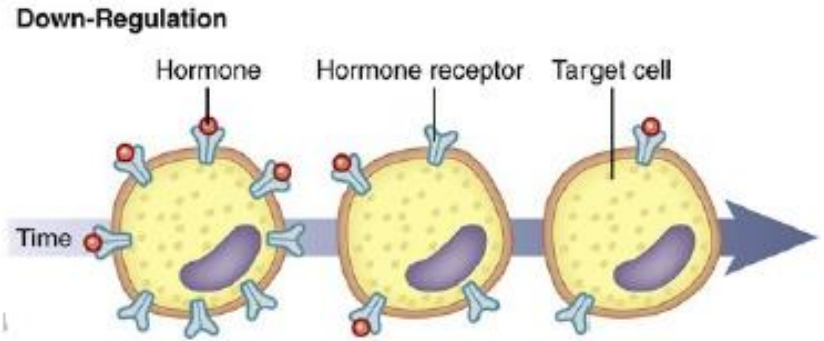
2. Elevated levels of serum free fatty acids (FFAs) and intracellular deposits of triglycerides and cholesterol are also found in obese individuals. These changes interfere with intracellular insulin signaling, decrease tissue responses to insulin, and promote inflammation.

3. Inflammatory cytokines are released from intra-abdominal adipocytes or adipocyte-associated mononuclear cells and induce insulin resistance and are cytotoxic to beta cells.

4. Obesity is correlated with hyperinsulinemia and decreased insulin receptor density.

Prolonged stimulation of receptors may lead to a decrease in the number of receptors for insulin present on body cells.

This decrease is called downregulation.



Glucagon concentration is increased in type 2 diabetes because pancreatic alpha cells become less responsive to glucose inhibition

Clinical manifestations Type 2 Diabetes Mellitus

The affected individual is often:

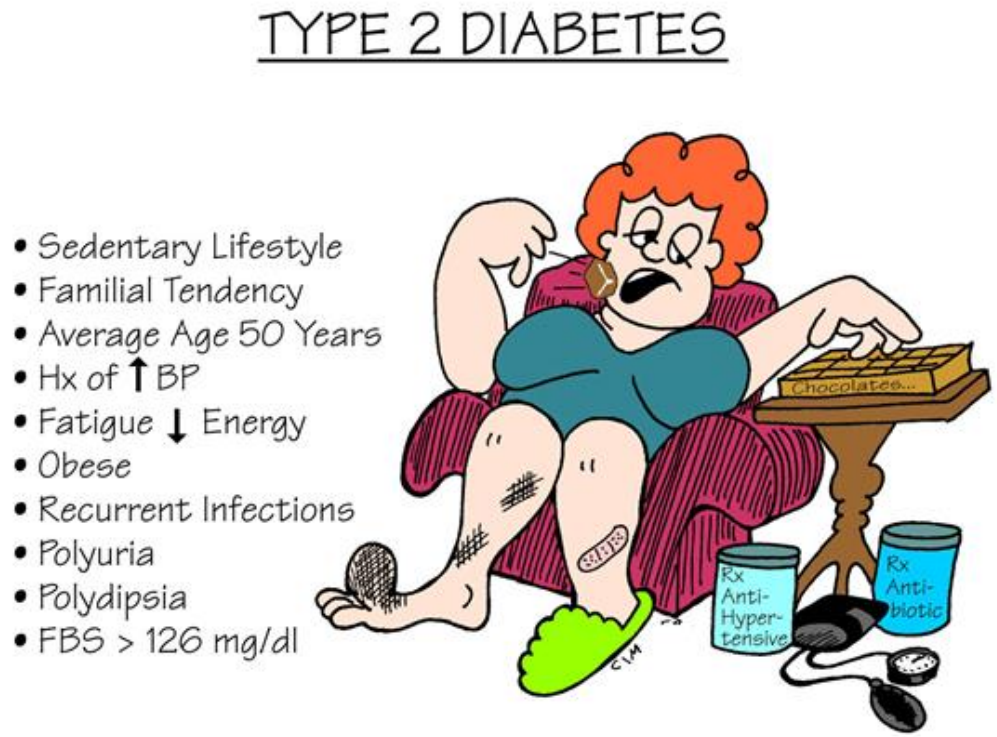
1- Overweight.
2- Dyslipidemic.
3- Hyperinsulinemic.
4- Hypertensive.

Also may show some classic symptoms of diabetes:

5- Polyuria and 6- Polydipsia.

But more often will have nonspecific symptoms such as:

7- Fatigue.
8- Pruritus.
9- Recurrent infections.
10- Visual changes.
11- Paresthesias or weakness.



Treatment

As with type 1 diabetes, the goal of treatment for individuals with type 2 diabetes is the restoration of a normal blood glucose level and correction of related metabolic disorders.

1- Maintaining an appropriate diet and exercise program.

2- Oral Hypoglycemic agents.

3- A combination of drugs may be required.

4- Insulin therapy may be needed in the later stage of type 2 diabetes because of loss of beta-cell function, which is progressive over time.

Other Specific Types of Diabetes Mellitus

The best-described of these other specific types of diabetes is termed
maturity-onset diabetes of youth (MODY).

MODY includes six specific autosomal dominant mutations that affect critical enzymes involved in beta-cell function or insulin action.

Diagnosis and management are similar to those techniques used for type 2 diabetes.

Gestational diabetes mellitus (GDM) has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy.

GDM complicates approximately 7% of all pregnancies.
Screening for GDM is recommended in asymptomatic, pregnant women after 24 weeks of gestation. An OGTT is used to confirm the diagnosis.

Careful glucose control prenatally, during pregnancy, and after delivery is essential to the short- and long-term health of both mother and baby.

Women who have GDM have a greatly increased subsequent diabetes risk, making consistent follow-up important

Acute Complications of Diabetes Mellitus

1- **Hypoglycemia:** is a blood glucose level less than **50 mg/l00 mL** of blood.

can be caused by fasting or, especially, fasting coupled with exercise, because exercise increases the usage of glucose by skeletal muscle.

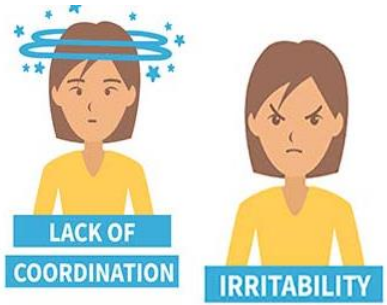
Hypoglycemia in diabetes is sometimes called insulin shock or insulin reaction.

It most common in Individuals with type 1 diabetes

Hypoglycemia does occur in type 2 diabetes when treatment involves insulin secretogogues (e.g., sulfonylureas) or exogenous insulin.

Symptoms include:

Because the brain relies on blood glucose as its main energy source, hypoglycemia results in many symptoms of altered central nervous system (CNS) functioning, including
confusion,
irritability,
anxiety,
seizure,
and coma.



headache, as a result of alteration of cerebral blood flow, and changes in water balance.

hypoglycemia causes activation of the sympathetic nervous system.
Tremor , pallor
stimulating hunger,
nervousness,
sweating,
and tachycardia.

Treatment requires immediate replacement of glucose either orally or intravenously.

Glucagon for home use can be prescribed for individuals who are at high risk

Diabetic ketoacidosis (DKA) is a serious complication related to a deficiency of insulin and an increase in the levels of insulin counterregulatory hormones (catecholamines, cortisol, glucagon, growth hormone)

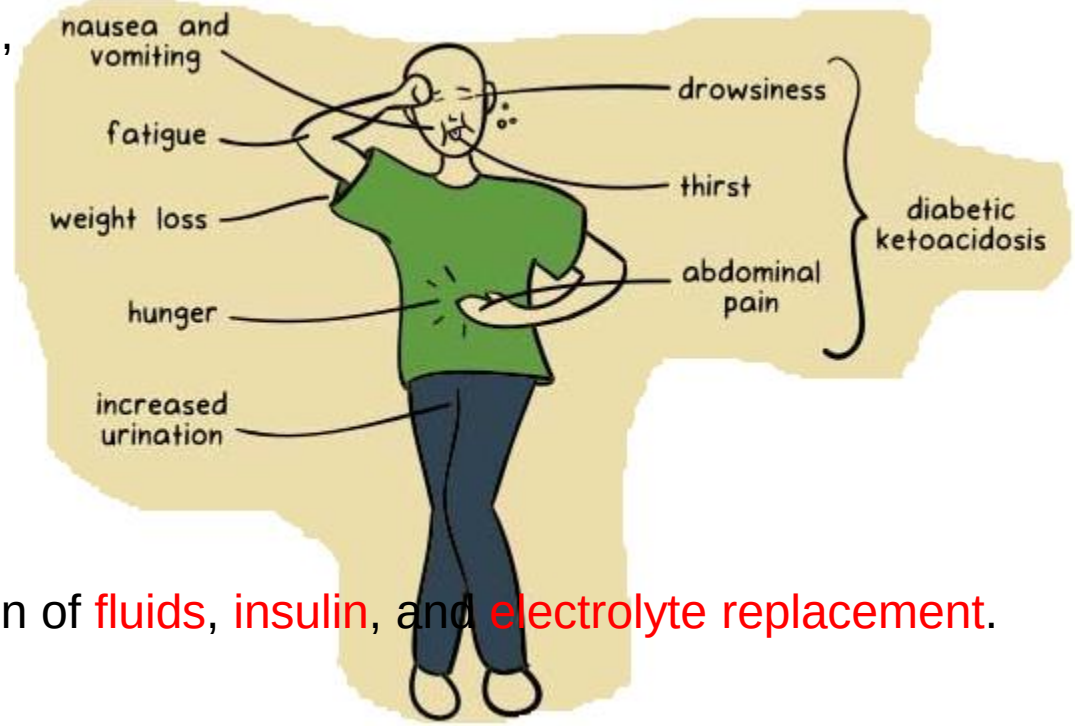
It is characterized by hyperglycemia, acidosis, and ketonuria.

insulin deficiency causes lipolysis and increased glyconeogenesis which contributing to hyperglycemia and production of ketone bodies at a rate that exceeds peripheral use.

Accumulation of ketone bodies causes a drop in pH, resulting in metabolic acidosis.

Symptoms of diabetic ketoacidosis include

Hyperventilation in an attempt to compensate for the acidosis,
postural dizziness,
central nervous system depression,
ketonuria,
anorexia,
nausea,
abdominal pain,
thirst, and polyuria.



Treatment

DKA is managed with a combination of fluids, insulin, and electrolyte replacement.

Chronic Complications of Diabetes Mellitus

Microvascular Disease

Diabetic microvascular complications (disease in capillaries) are a leading cause of blindness, end-stage kidney failure, and various neuropathies.

Hypoxia and ischemia accompany microvascular disease, especially in the eye, kidney, and nerves.

Many individuals with type 2 diabetes will present with microvascular complications because of the long duration of asymptomatic hyperglycemia that generally precedes diagnosis.

Diabetic retinopathy

Diabetic retinopathy results from relative hypoxemia, damage to retinal blood vessels, red blood cell (RBC) aggregation, and hypertension

The three stages of retinopathy that lead to loss of vision are:
1- nonproliferative (stage I), characterized by an increase in retinal capillary permeability, vein dilation, microaneurysm formation, and superficial and deep hemorrhages.

2- preproliferative (stage II), a progression of retinal ischemia with areas of poor perfusion that culminate in infarcts; and

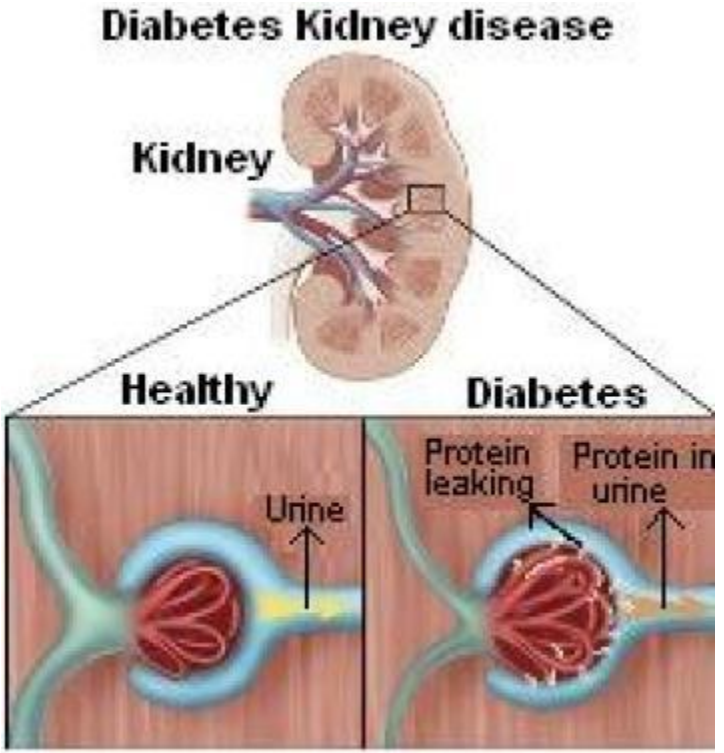
3- proliferative (stage III), the result of angiogenesis and fibrous tissue formation within the retina or optic disc.

Macular edema is the leading cause of blurred vision among persons with diabetes.

Diabetic nephropathy

nephropathy start with microalbumineurea after glomerular hyperfilteration (enlarged kidney followed by glomerular sclerosis) in which protienurea < 300 micg. (macroprotienurea > 300 micg.).

DM is the most common cause of Renal failure.

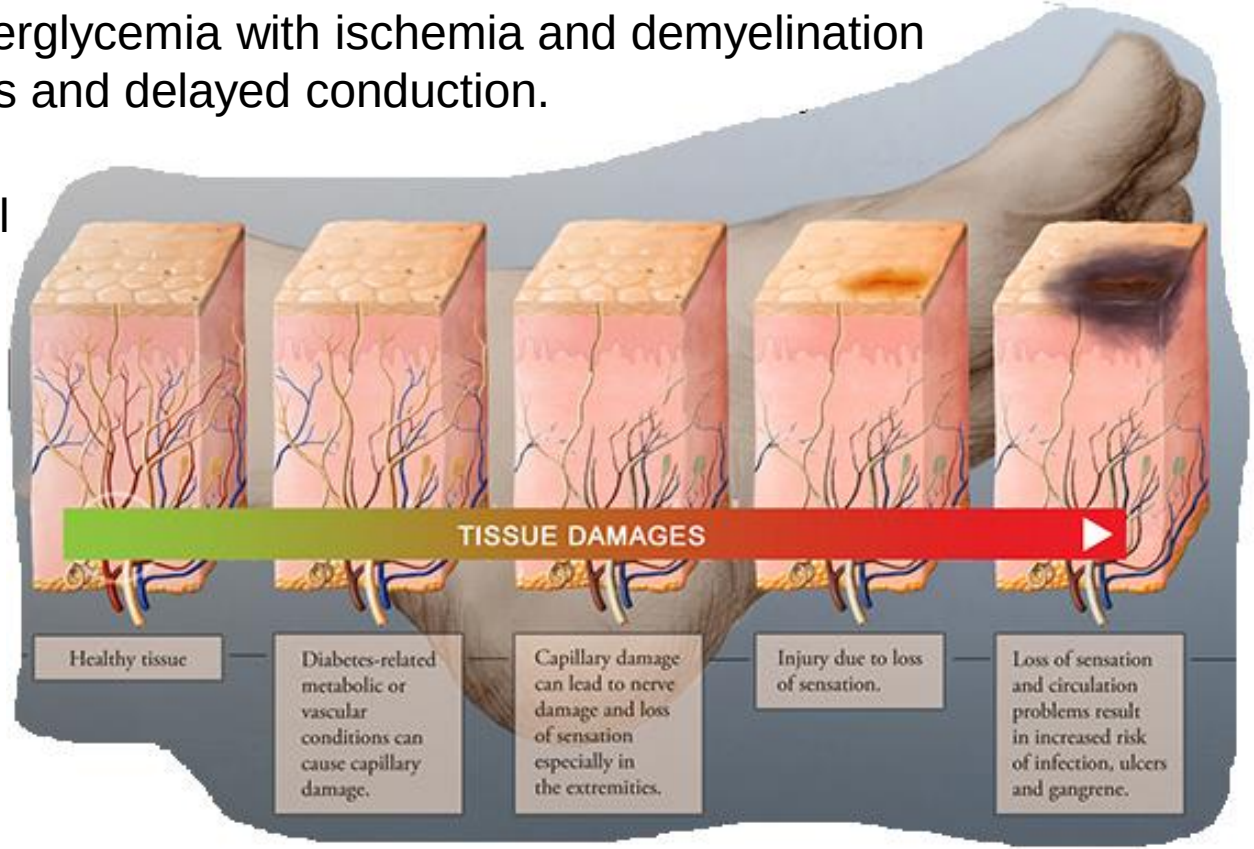


Diabetic neuropathies

The underlying pathologic mechanism includes both metabolic and vascular factors related to chronic hyperglycemia with ischemia and demyelination contributing to neural changes and delayed conduction.

Both somatic and peripheral nerve cells show diffuse or focal damage, resulting in polyneuropathy.

Loss of pain, temperature, and vibration sensation is more common than motor involvement and often involves the extremities first in the hands and feet.



Macrovascular Disease

Macrovascular disease (lesions in large- and medium-sized arteries) increases morbidity and mortality and increases risk for hypertension, accelerated atherosclerosis, cardiovascular disease, stroke, and peripheral vascular disease, particularly among individuals with type 2 diabetes mellitus.

Cardiovascular disease.

Cardiovascular disease is the ultimate cause of death in up to 68% of people with diabetes, with higher risk for women

Mechanisms of disease include:

vessel injury related to insulin resistance and hyperglycemia oxidative stress, accelerated atherosclerosis associated with high levels of triglycerides, high levels of small low-density lipoproteins (LDLs), and low levels of high-density lipoproteins (HDLs); platelet activation and prothrombosis; and endothelial cell dysfunction.

In general, the prevalence of Coronary artery disease increases with the duration but not the severity of diabetes and the onset can be silent.


Thank You