DIABETES

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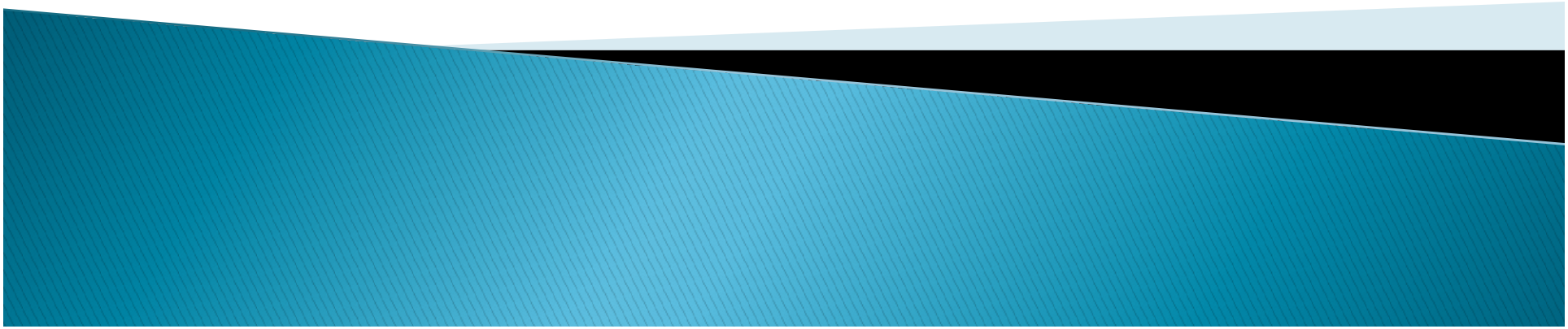


AN INTRODUCTION TO DIABETES MELLITUS

DEFINATION AND EPIDEMIOLOGY

As per the WHO, ***Diabetes Mellitus (DM) is defined as a heterogeneous metabolic disorder characterized by common feature of chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism.***

•DM is leading cause of morbidity and mortality world over.

•It is expected to continue as a major health problem owing to its serious complications, especially end stage renal disease, IHD, gangrene of the lower extremities, and blindness in adults.

•Top 5 countries with highest prevalence of DM are India, China, US, Indonesia and Japan.

•In India, its incidence is estimated at 7% of adult population (approximately 65 million affected people), largely due to genetic susceptibility combined with changing life style of low-activity high-calorie diet in the growing Indian middle class.

• It is anticipated that by the year 2030 the number of **diabetics** globally will double from the present figure of 250 million

CLASSIFICATION & ETIOLOGY

Classification of DM based on etiology (as per American Diabetes Association, globally accepted standards)

TYPE 1A DIABETES MELLITUS (10%)

(Earlier called insulin-dependent, or juvenile-onset diabetes)

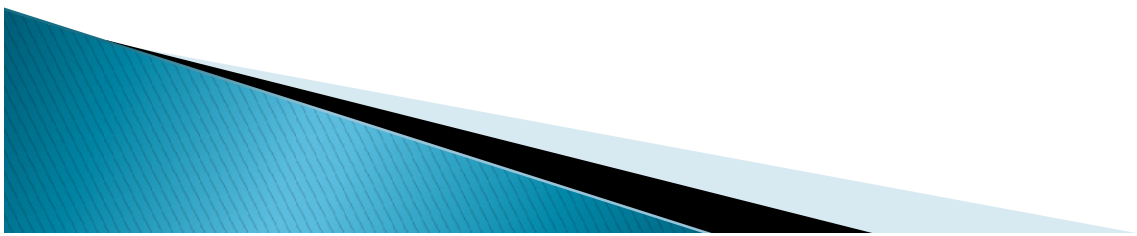
- TYPE 1A DM : Immune-mediated
- TYPE 1B DM : Idiopathic

TYPE 2 DIABETES MELLITUS (80%)

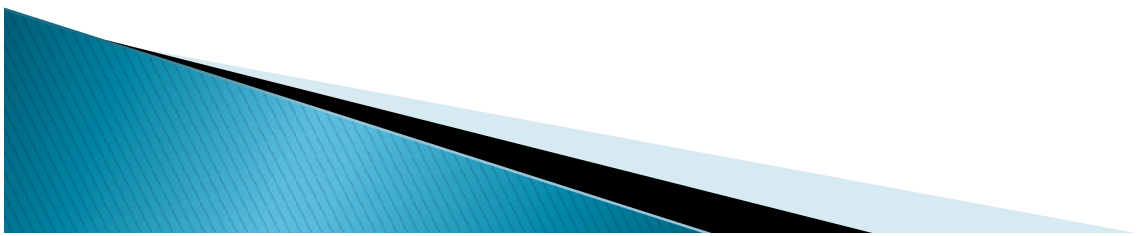
(Earlier called non-insulin-dependent, or maturity-onset diabetes)

OTHER SPECIFIC TYPES OF DIABETES (10%)

- Genetic defect of -cell function due to mutations in various enzymes (example: hepatocyte nuclear transcription factor-HNF, glucokinase)
- Genetic defect in insulin action (example: type A insulin resistance)
- Diseases of exocrine pancreas (example: chronic pancreatitis, pancreatic tumors, post-pancreatectomy)
- Endocrinopathies (example: acromegaly, Cushing's syndrome, pheochromocytoma)



- Drug or chemical induced (example: steroids, thyroid hormone, thiazides, -blockers, etc)
- Infections (example: congenital rubella, cytomegalovirus)
- Uncommon forms of immune-mediated DM (stiff man syndrome, anti-insulin receptor anti-bodies)
- Other genetic syndromes (example: Down's syndrome, Klinefelter's syndrome, Turner's syndrome)



GESTATIONAL DIABETES (4%)

About 4% of pregnant women develop DM due to metabolic changes during pregnancy. Although they revert back to normal glycaemia after delivery, these women are prone to develop DM later in their life.

MAJOR RISK FACTORS

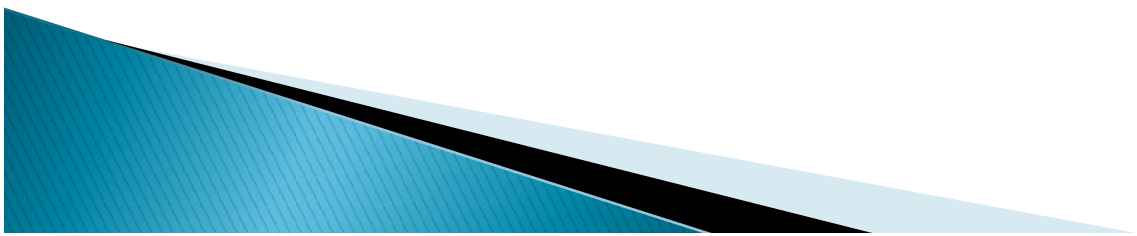
1. Family history of Type 2 DM
2. Obesity
3. Habitual physical inactivity
4. Race and ethnicity (Blacks, Asians, Pacific Islanders)
5. Previous identification of impaired fasting glucose or impaired glucose tolerance
6. History of gestational DM or delivery of baby heavier than 4 kg
7. Hypertension
8. Dyslipidaemia (HDL level < 35 mg/dl or triglycerides > 250 mg/dl)
9. Polycystic ovary disease and acanthosis nigricans
10. History of vascular disease

PATHOGENESIS

Depending upon etiology of DM, hyperglycemia may result from the following:

- **Reduced insulin secretion**
- **Decreased glucose use by the body**
- **Increased glucose production**

In order to understand it properly, it is essential to first recall physiology of normal insulin synthesis and secretion.



Insulin is a polypeptide hormone with 51 amino acids having two chains. i.e., A-chain and B-chain. The A-chain has 21 amino acids. The B-chain has 30 amino acids.

Insulin is secreted by rough endoplasmic reticulum of beta cells as preproinsulin.

Preproinsulin

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Proinsulin

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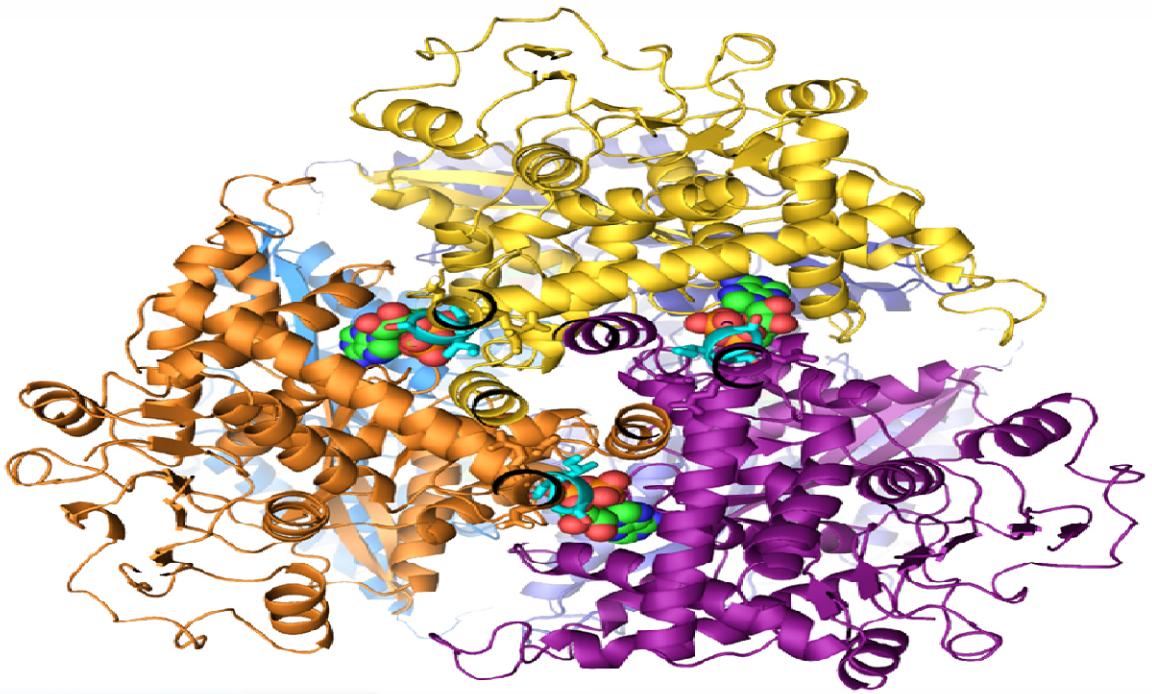
Insulin

Insulin circulates in blood in an unbound form.

Plasma half-life is 5 minutes.

MECHANISM OF ACTION OF INSULIN



-Insulin binds to the insulin receptors which are present mainly in the liver, skeletal muscle and adipose tissue.

-The insulin receptors are large membrane proteins with two alpha and two beta subunits.

-They are bound to each other by disulfide bridges. The insulin receptors are located on chromosome 19.

- Binding of insulin to alpha subunits to bring about conformational change in beta subunits.

- Conformational change in beta subunits activates tyrosine kinase activity producing autophosphorylation of beta subunits.

- This leads to phosphorylation of intracellular enzymes including a group of enzymes called insulin receptor substrates (IRS).

- IRS causes a variety of changes like activation or deactivation of target enzymes, translocation of GLUTs (Glucose Transporters), and induction or suppression of genes.

In this way, insulin produces required effects on carbohydrate, fat and protein metabolism.

DEGRADATION

Insulin is cleared from circulation every 10-15 minutes

It is destroyed by *insulin protease* in the liver and kidney.

ACTIONS OF INSULIN

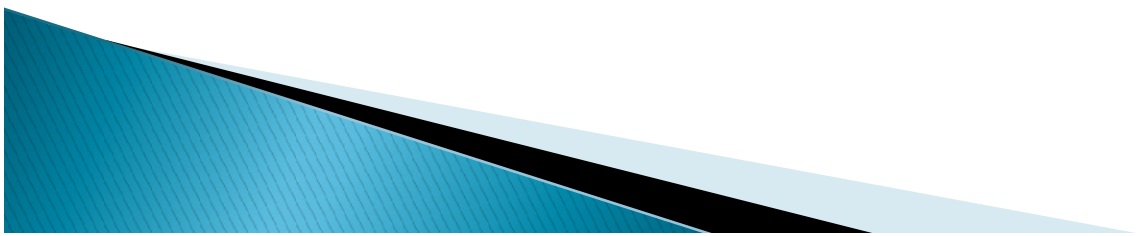
Rapid: Increases transport of glucose, amino acids, and potassium ions (K^+) into insulin-sensitive cells

Intermediate: Stimulates protein synthesis; inhibits protein degradation.

Delayed: Increases the formation of mRNA for lipogenic action.

FUNCTIONS

Insulin has a wide range of activities that are broadly divided into two groups: **Metabolic functions** and **effect on growth**.



METABOLIC FUNCTIONS

- ***Carbohydrate Metabolism***

Helps in cellular uptake of glucose.

Increases peripheral utilization of glucose.

Prevents glycogenolysis and neoglucogenesis, and improves glycogen synthesis.

- ***Protein Metabolism***

Facilitates the transport of amino acids into the cells.

Increases mRNA translation.

Increases protein synthesis.

Prevents protein breakdown.

Hence it is an anabolic hormone.

- ***Lipid Metabolism***

Prevents lipolysis by inhibiting hormone-sensitive lipase.

Decrease free fatty acid in the blood.

Promotes the synthesis and storage of fats.

Ion Transport

Insulin increases potassium ion transport into the cell.

Growth and Development

Insulin potentiates the action of growth hormone to promote growth.

Insulin and growth hormone act synergistically to promote growth

REGULATION of INSULIN

Factors enhancing insulin release

- Increased levels of glucose, amino acid, GI hormones, glucagon and parasympathetic stimulation.

Factors reducing insulin release

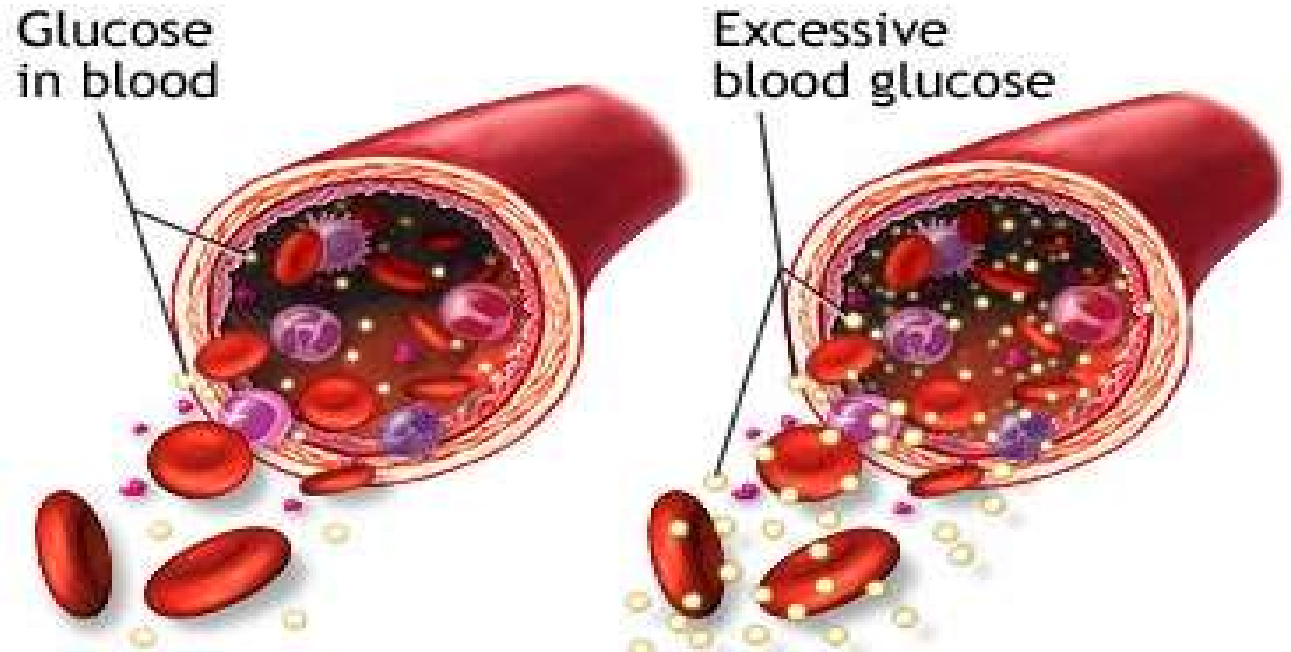
- Increased secretion of somatostatin and sympathetic stimulation.
- Control of insulin secretion is brought about by blood glucose concentration.
- Insulin secretion increases as the concentration of blood glucose increases. This increases the transport of glucose into liver, muscles and other cells, thereby reducing the blood glucose concentration towards normal.
- Amino acids like arginine and lysine also stimulate insulin secretion.
- **G**astrin, secretin, cholecystokinin (CCK), and gastric **inhibitory p**olypeptide (GIP) cause a moderate increase in **insulin secretion**.

CONTROL OF INSULIN SECRETION

- The serum insulin levels rise within 10 minutes after the ingestion of food.
- It reaches peak in 30-45 minutes.
- When stimulated, insulin is released in two phases: early phase due to release of preformed insulin and late phase due to the release of the newly formed insulin.
- Insulin increases the uptake, storage and utilization of glucose in almost all the tissues of the body. Muscles, adipose tissues and liver utilize glucose under the influence of insulin.
- Brain, RBC, kidney and mucosa of small intestine are not dependent on insulin for the uptake and utilization of glucose.

CLINICAL FEATURES DIABETES MELLITUS

Hyperglycemia in DM does not cause a single disease but is associated with numerous diseases and symptoms, especially due to complications



Clinical features of TYPE 1DM

1. Patients of type1 DM usually manifest at early age, generally before age of 35.
2. The onset of symptoms is often abrupt
3. These patients present with:

- ***Polyuria (increased urination):*** increased blood glucose levels caused increased excretion of glucose in urine. This causes excessive excretion of water due to the osmotic effect of glucose.
- ***Polydipsia (increased thirst):*** increased excretion of urine leads to decreased body water levels. This causes the sensation of thirst, resulting in increased water intake.
- ***Polyphagia (increased hunger):*** there is reduced entry of glucose into glucostatic cells due to lack of insulin. This suppresses the satiety centre and stimulates the feeding centre, enhancing the desire to eat.

Polyuria, Polydipsia & Polyphagia

Polyuria: excessive urination, Polydipsia: excessive thirst
Polyphagia: excessive hunger. **Combination of these 3 is one of the major symptoms of Diabetes Mellitus**

Excessive Urination

Excessive Thirst

Excessive Hunger

4. Progressive loss of weight.
5. These patients are prone to develop metabolic complications such as ketoacidosis and hyperglycemic episodes.
6. Delayed wound healing.

Clinical features of TYPE 2 DM

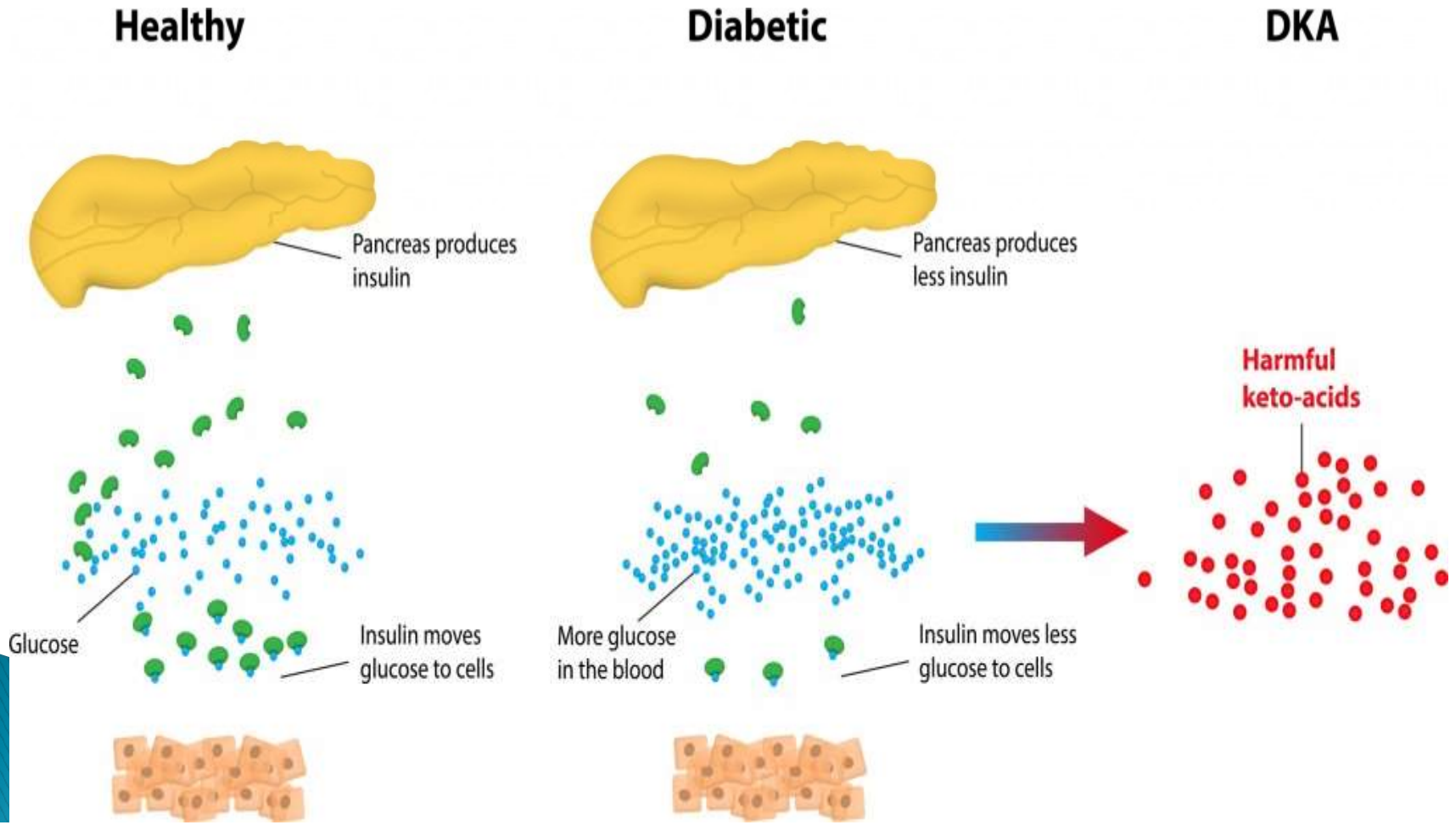
1. This form of DM generally manifests in the middle life or beyond, usually above age of 40.
2. The onset of symptoms in type2 DM is slow and insidious.
3. Generally the patient is asymptomatic when the diagnosis is made on the basis of glucosuria, or may present with polyuria and polydipsia.
4. Patients are frequently obese and have unexplained weakness and loss of weight.
5. Metabolic complications like ketoacidosis, common in **Type 1** are not frequently seen in Type 2.

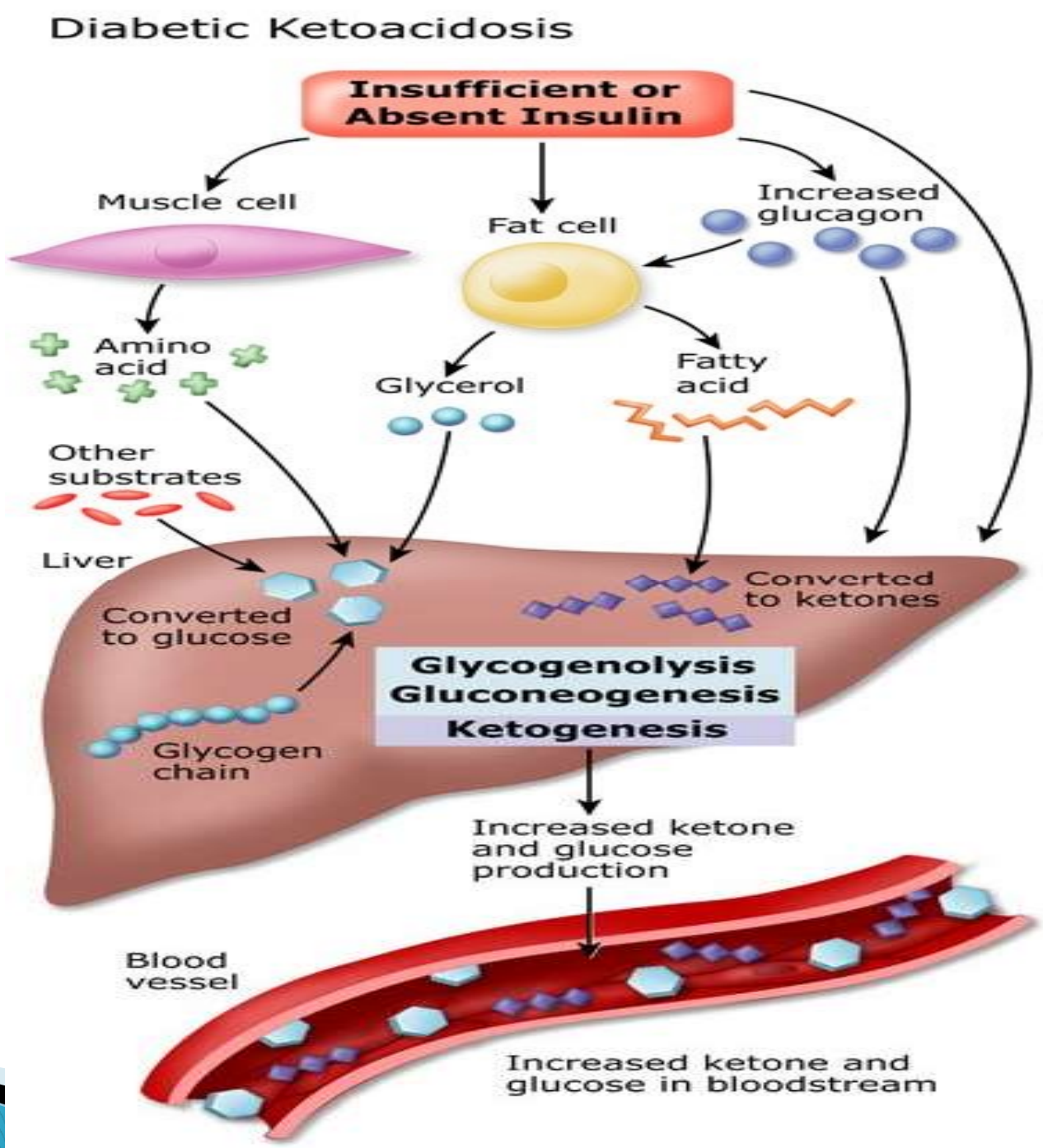
COMPLICATIONS OF DM

As a consequence of hyperglycemia of DM, every tissue and organ of the body undergoes biochemical and structural alteration s which account for the major complications in diabetes which may be ***acute metabolic*** or ***chronic systemic.***

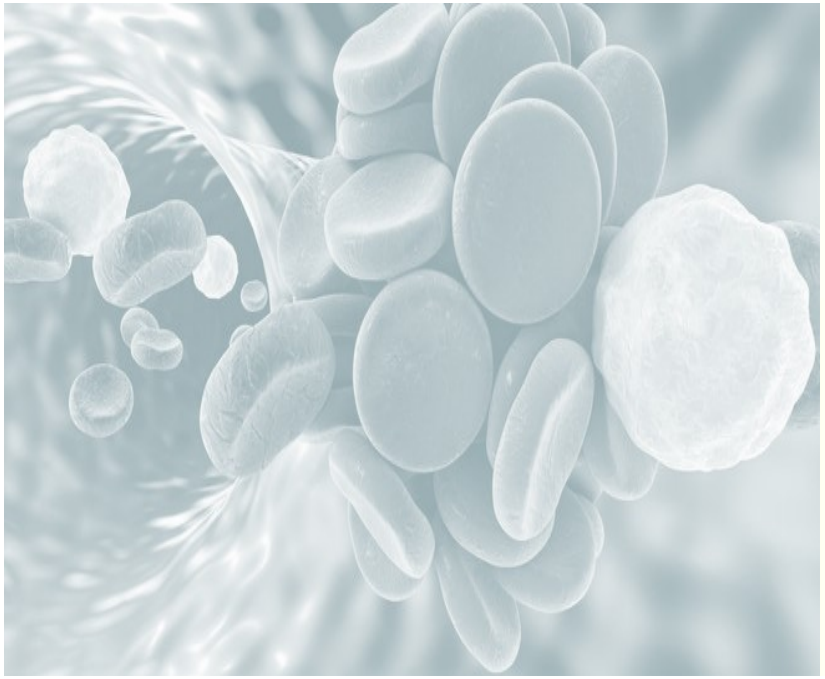
Acute Metabolic complications

- ***Diabetic Ketoacidosis*** and ***systemic metabolic ketoacidosis*** caused due to excess ketone bodies. Clinically characterized by anorexia, nausea, vomiting, deep and fast breathing, mental confusion and coma.

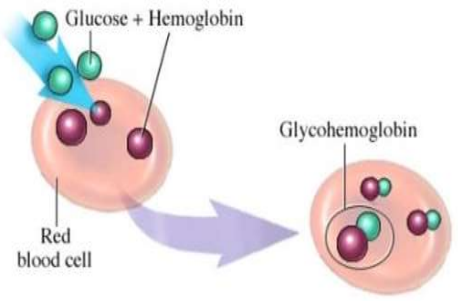


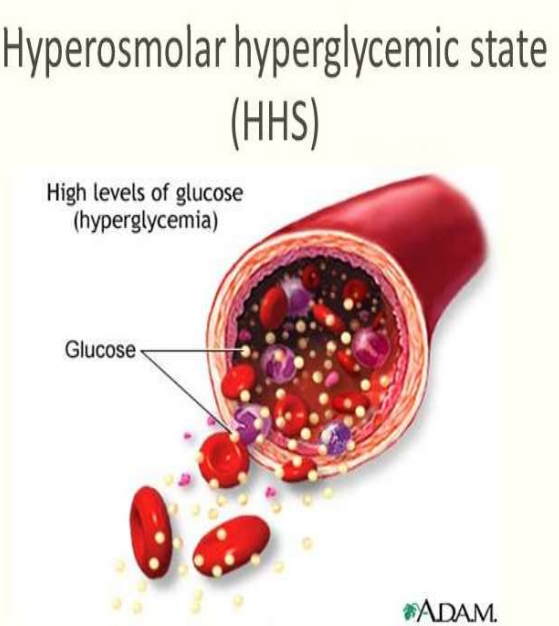

Diabetic Ketoacidosis
Insufficient or Absent Insulin
Muscle cell
Fat cell
Increased glucagon
Amino acid
Glycerol
Fatty acid
Other substrates
Liver
Converted to glucose
Converted to ketones
Glycogenolysis
Gluconeogenesis
Ketogenesis
Glycogen chain
Increased ketone and glucose production
Blood vessel
Increased ketone and glucose in bloodstream

- ***Hyperosmolar non-ketotic coma*** caused due to severe dehydration resulting from sustained hyperglycemic dieresis. Characterized by extremely high blood sugar and high plasma osmolality. ***Thrombotic*** and ***bleeding complications*** are high due to viscosity of blood. Mortality rates are high in people presenting with these complications.
- ***Hypoglycemic episodes*** leading to permanent brain damage or rebound hyperglycemia



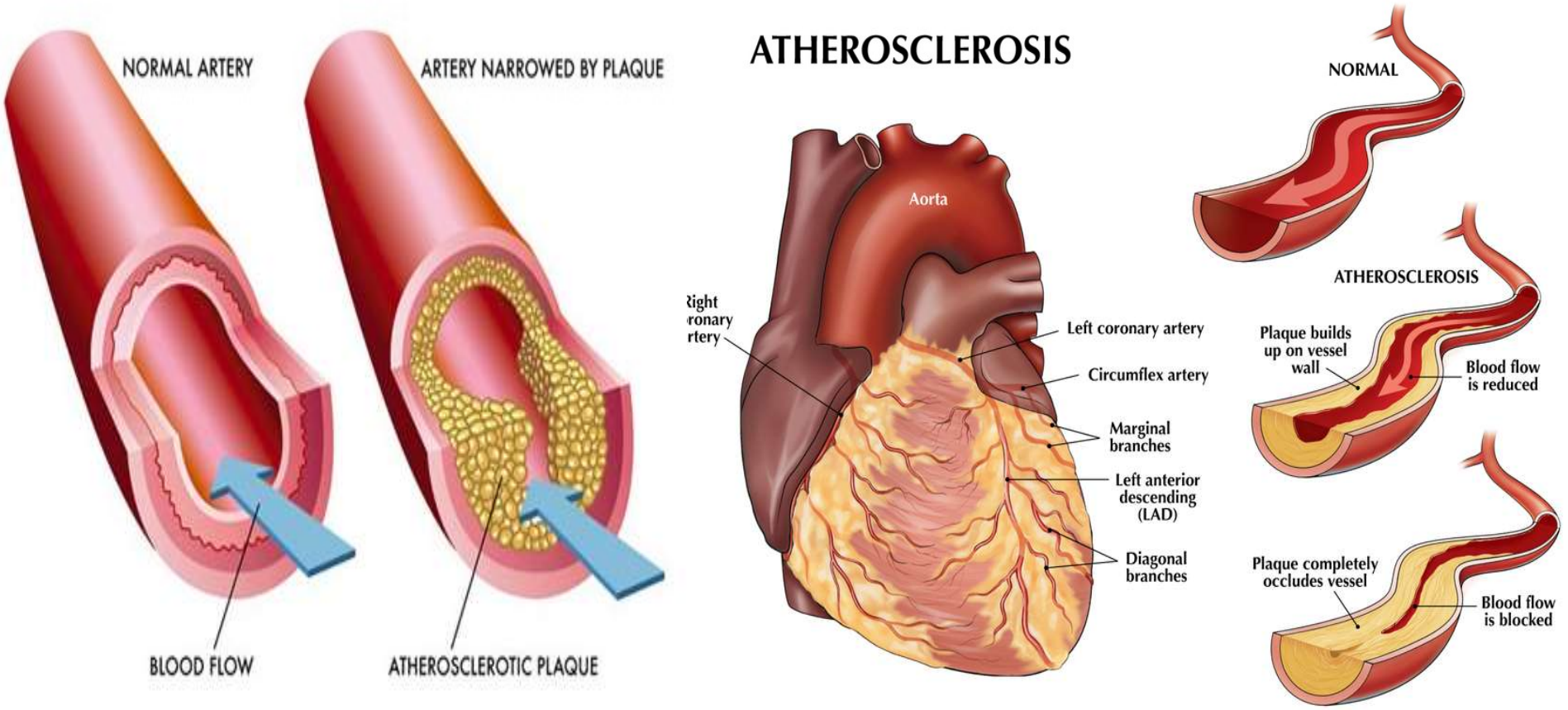
Hypoglycemia





Late systemic complications

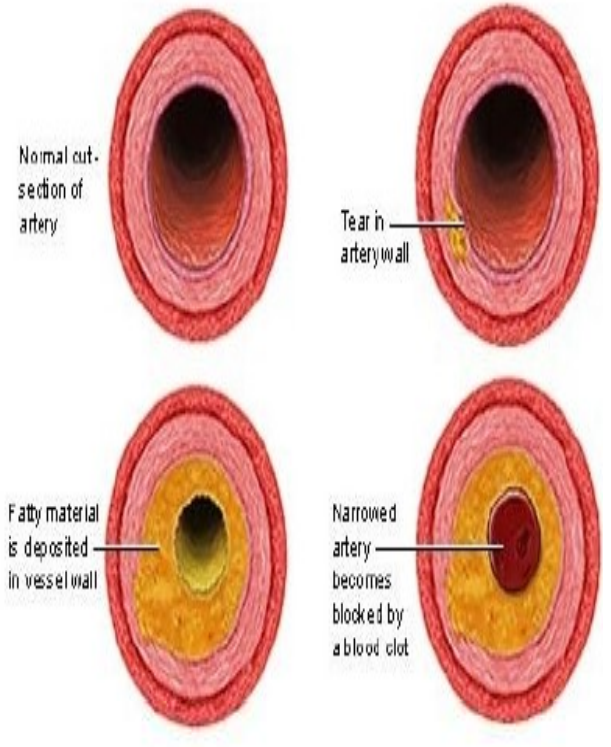
- ***Atherosclerosis*** involving complicated plaques such as calcification and thrombosis is seen leading to early onset of coronary artery disease, silent myocardial infarction, cerebral stroke and gangrene of toes and feet.



- ***Diabetic microangiopathy*** characterized by thickening of membranes of small blood vessels and capillaries of different organs and tissues such as skin, skeletal muscle, eye and kidney.

Macroangiopathy = damage to larger blood vessels

Atherosclerosis = clogging of the blood vessels



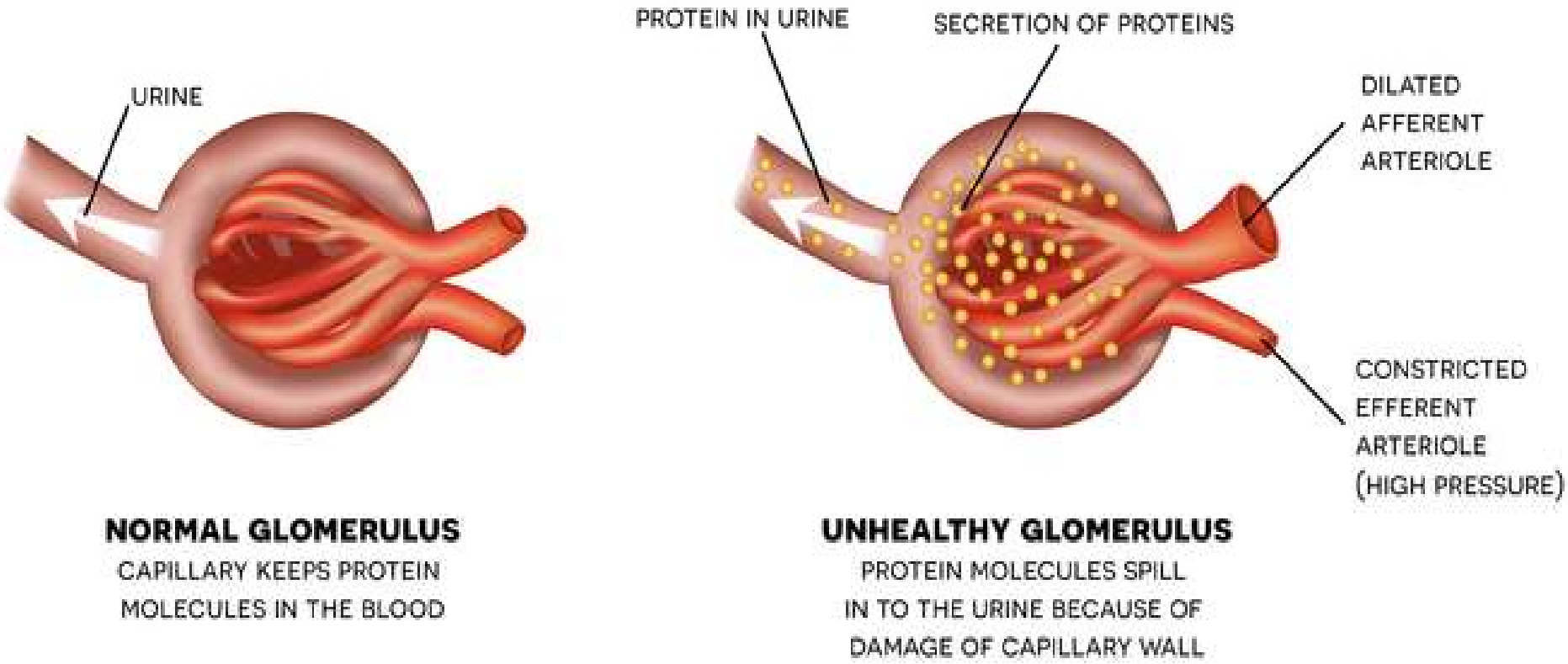
At early stage

Reversible changes :
- ↑ Capillary press .
- ↑ Blood flow .
- ↑ EC permeability .

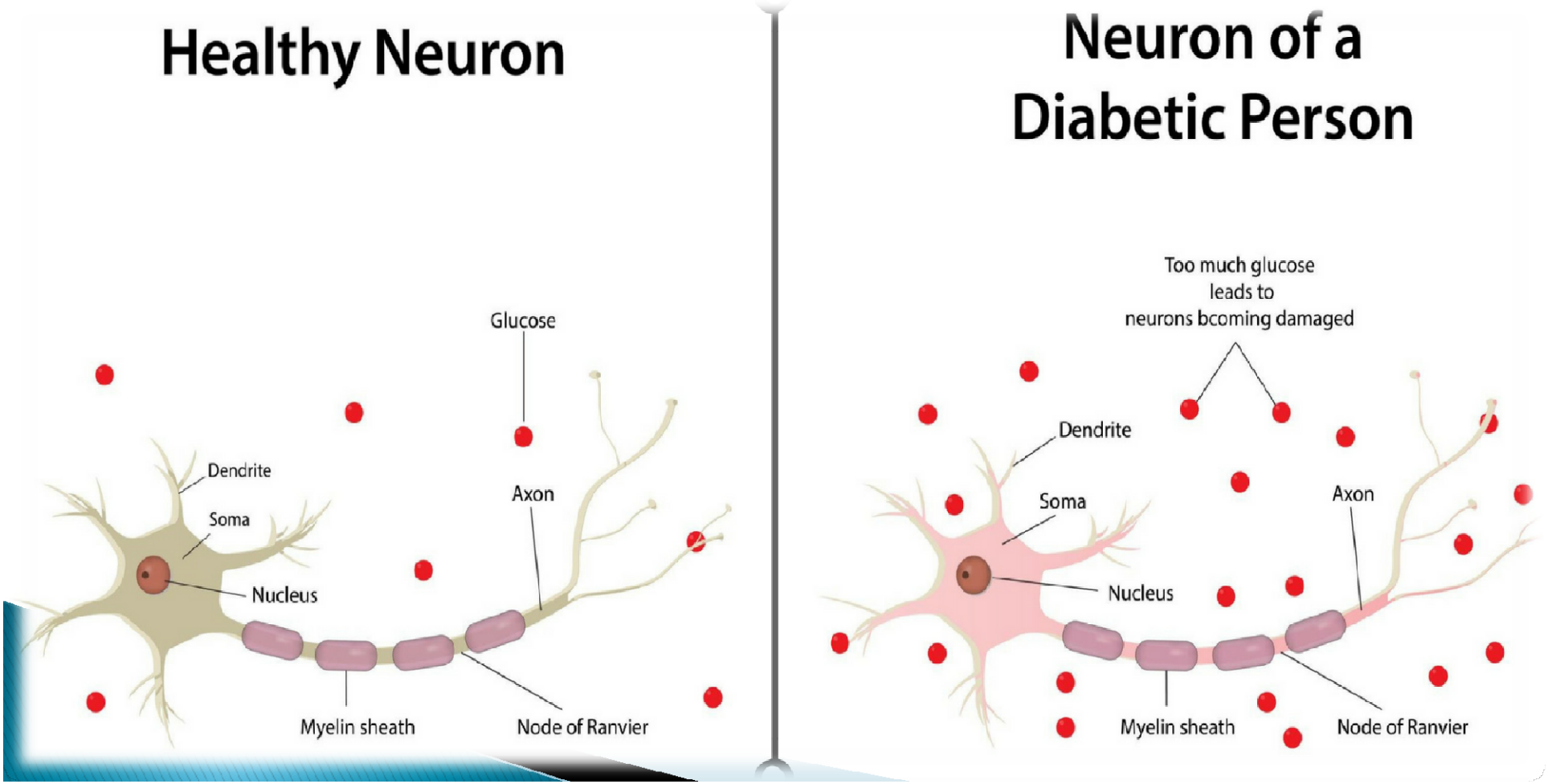
At later stages

Irrevesible changes :
- Thickening of the basement membrane
- Extracellular accumulation of proteins

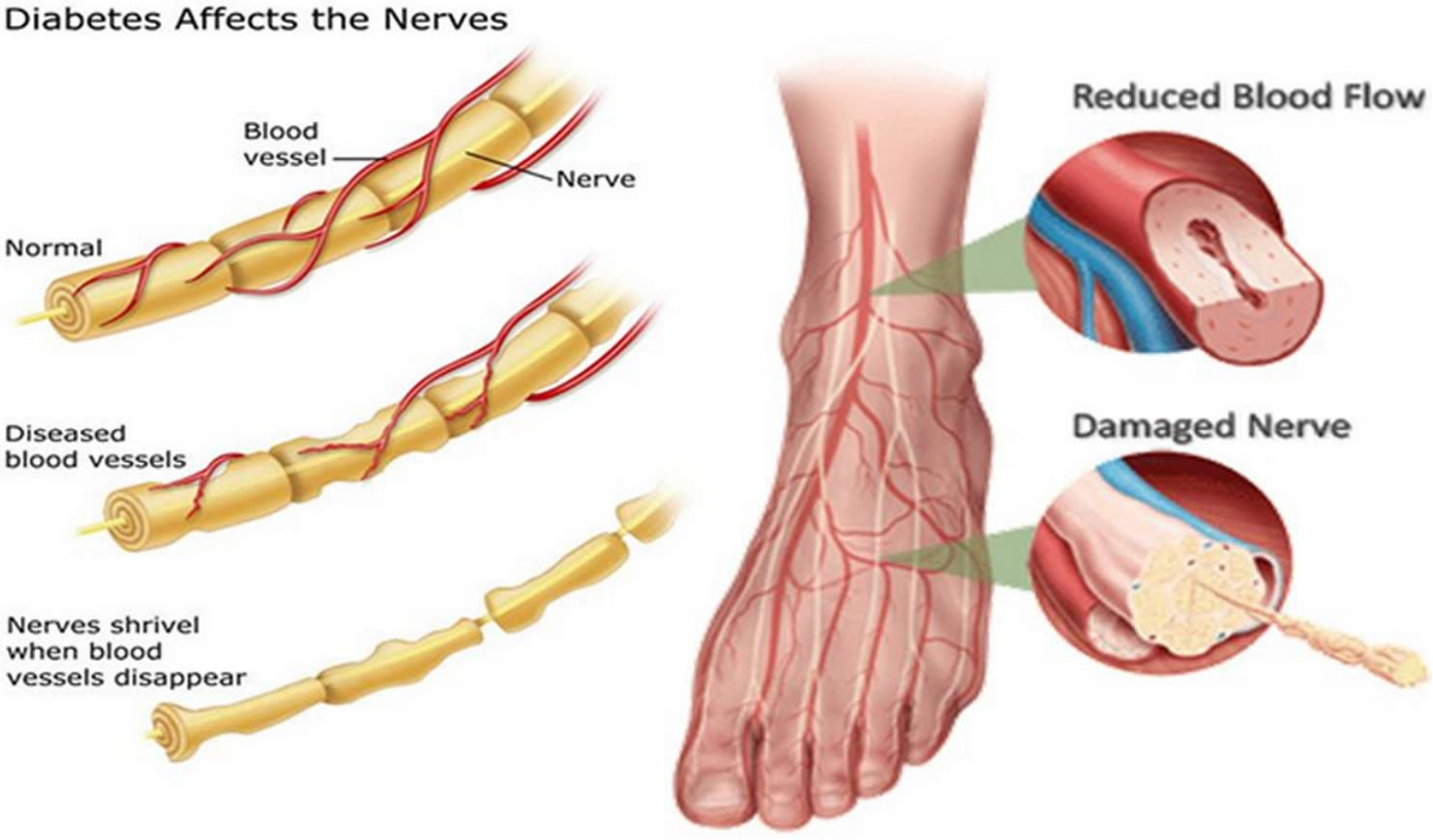
- ***Diabetic nephropathy*** characterized by different types of lesions leading to renal involvement is a common complication and a leading cause of death in diabetes.



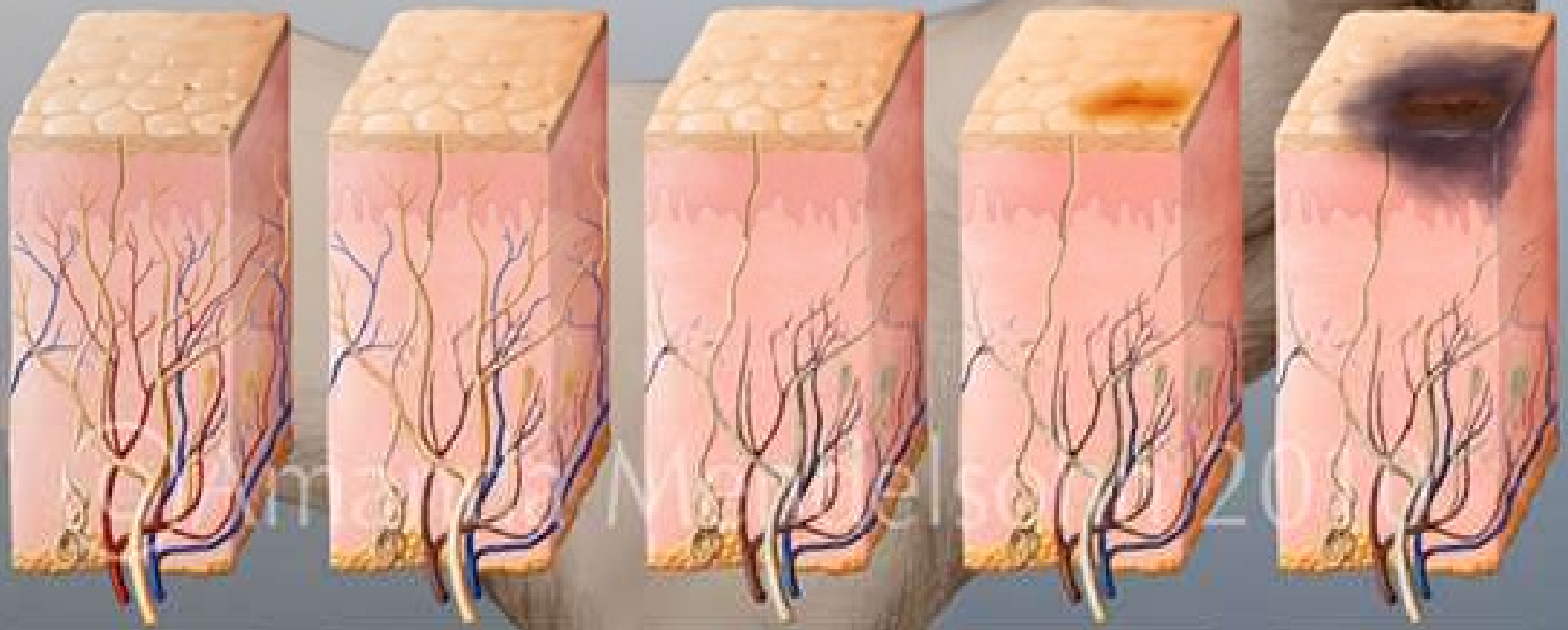
- ***Diabetic neuropathy*** affects all parts of nervous system but systemic peripheral neuropathy is most often seen. The basic pathological changes are segmental demyelination, Schwann cell injury and axonal damage of the neurons.



Diabetic Neuropathy



Diabetic Peripheral Neuropathy



Healthy tissue

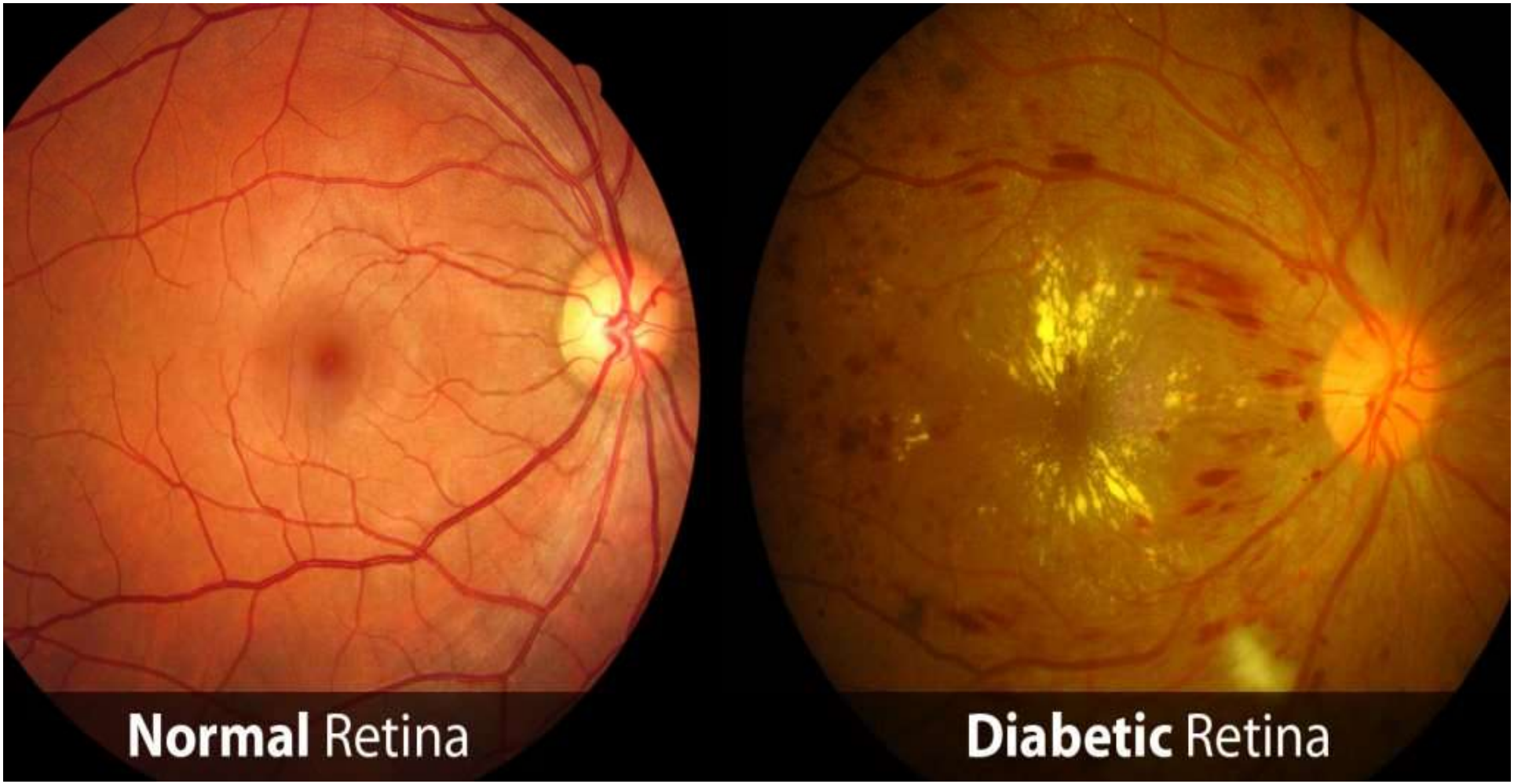
Diabetes-related metabolic or vascular conditions can cause capillary damage.

Capillary damage can lead to nerve damage and loss of sensation especially in the extremities.

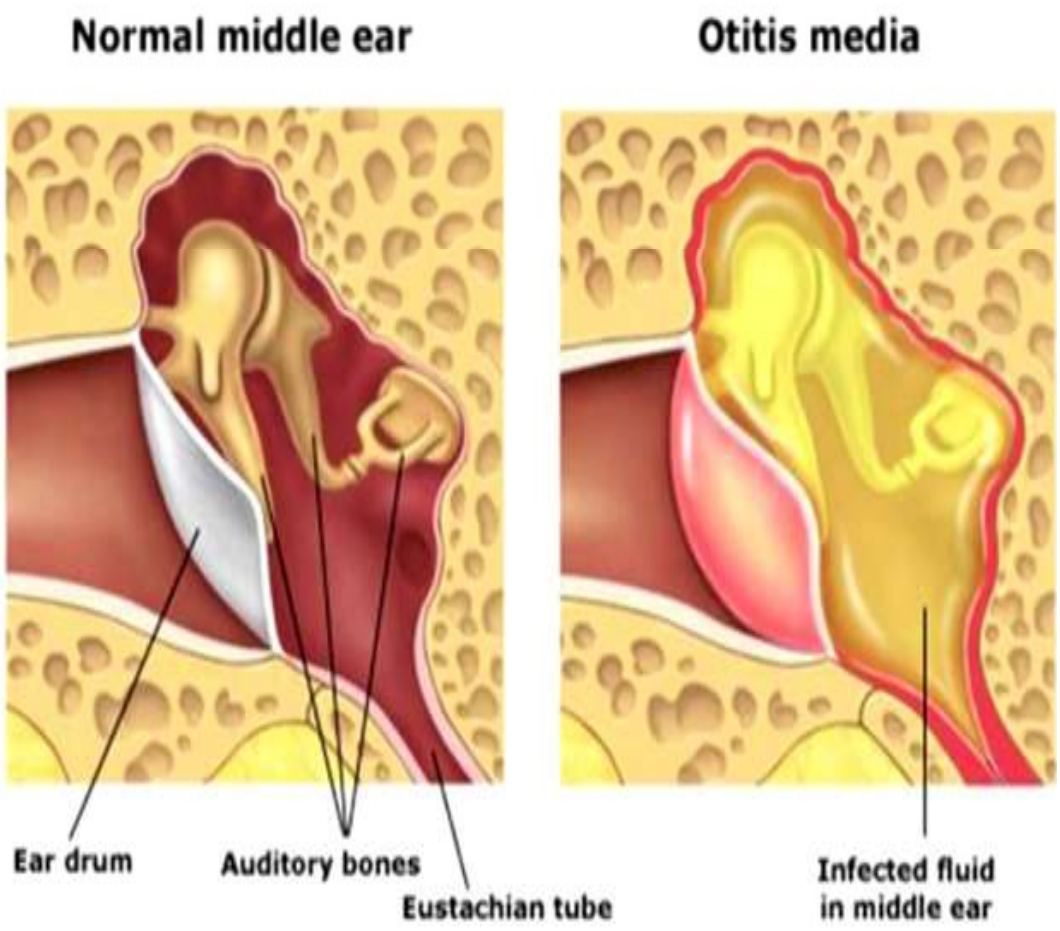
Injury due to loss of sensation.

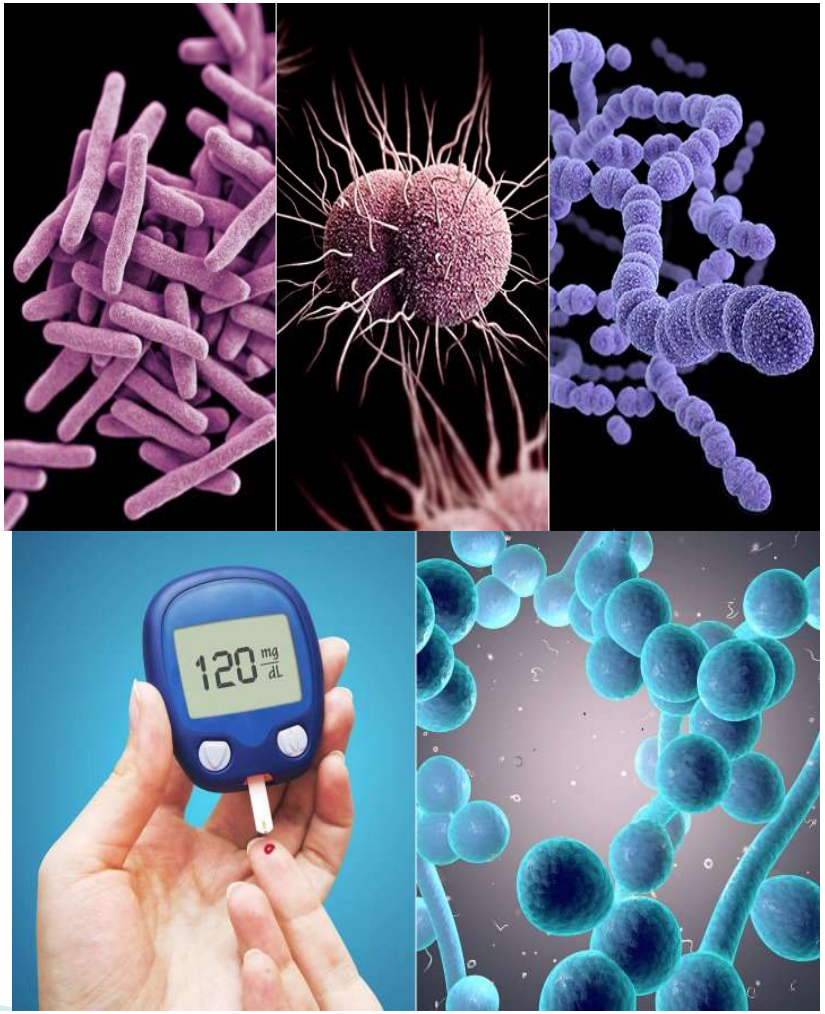
Loss of sensation and circulation problems result in increased risk of infection, ulcers and gangrene.

- ***Diabetic retinopathy*** causes lesions in the retinal vessels and is the leading cause of blindness. It also leads to early onset cataract and glaucoma.



- ***Infections*** like tuberculosis, pneumonia, pyelonephritis, otitis and diabetic ulcers are higher in patients of DM. this is due to various factors such as reduced cellular immunity, impaired leucocyte function and poor blood supply.





- Acupressure protocols will be added here.