Pathology and complications of Diabetes Mellitus

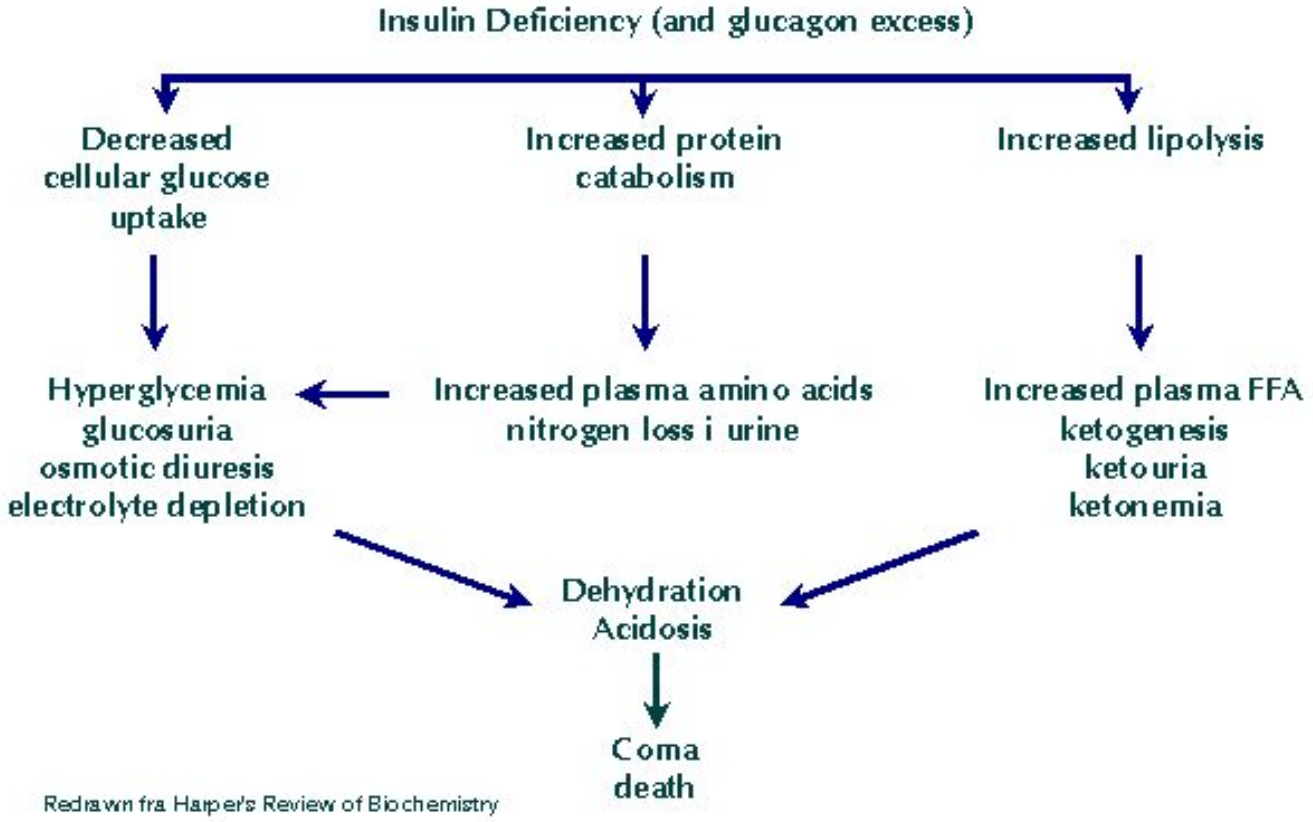
Learning objectives

1. Understand why good diabetic control reduces the incidence of long-term complications.
2. Differentiate between micro- and macrovascular damage, and the diseases they cause.
3. Understand the other complications that are associated with diabetes.
4. Identify some of mechanisms by which glucose can cause long-term complication of diabetes

Diabetes Mellitus

- Metabolic disease affecting CHO, protein and fat metabolism due to insulin deficiency or inefficiency.
- Two types: type I (insulin dependant) and Type II (insulin independent).

Diabetic Metabolism



Redrawn fra Harper's Review of Biochemistry

Complications of diabetes mellitus

I. Acute complications:

- diabetic ketoacidosis
- hypoglycemia
- diabetic nonketotic hyperosmolar coma

II. Chronic complications:

a. Microvascular

- retinopathy
- nephropathy
- neuropathy
- diabetic foot
- dermopathy

b. Macrovascular

- Cerbrovascular.
- Cardiovascular.
- peripheral vascular disease.

Diabetic ketoacidosis (DKA)

- May be the 1st presentation of type 1 DM.
- Result from absolute insulin deficiency or increase requirement.
- Mortality rate around 5%.

Pathophysiology of DKA

- Ketosis
- Dehydration
- Electrolyte imbalance

Diagnosis of DKA

- Hyperglycemia
- Ketonuria and ketonemia
- Acidosis (PH< 7.3)

Predisposing factors for DKA

- Infection
- Trauma
- Myocardial Infarction
- Stroke
- Surgery
- Emotional stress

Clinical presentation of DKA

- Polyurea and polydepsia.
- Nausea and vomiting.
- Anorexia and abdominal pain.
- Tachycardia.
- Fruity odor of the breath.
- Hypotonia, stupor and coma.
- Sign of dehydration.

Treatment of DKA

- Fluid replacement.
- Insulin therapy for hyperglycemia.
- Electrolyte correction.
- Acidosis correction.
- Treatment of precipitating cause.

Complication of DKA

- Cerebral edema
- Vascular thrombosis
- Infection
- M I
- Acute gastric dilatation
- Respiratory distress syndrome

Hypoglycemic coma

- Hypoglycemia is the most frequent acute complication in type 1 diabetes.

- Hypoglycemia is the level of blood glucose at which **autonomic** and **neurological** dysfunction begins

Clinical manifestations of hypoglycemia:

- **<u>Autonomic dysfunctions:</u>**
  1. Hunger
  2. Tremor
  3. Palpitation
  4. Anxiety
  5. Pallor
  6. Sweating

- **<u>Neurologic dysfunctions:</u>**
  1. Impaired thinking
  2. Change of mood
  3. Irritability
  4. Headache
  5. Convulsion
  6. Coma

Predisposing factors

- Missed meal
- Change in physical activity
- Alterations or errors in insulin dosage
- Alcohol ingestion

Treatment of hypoglycemia

- In mild cases oral rapidly absorbed carbohydrate
- In sever cases (comatose patient) iv hypertonic glucose 25% or 50% concentration
- Glucagons injection

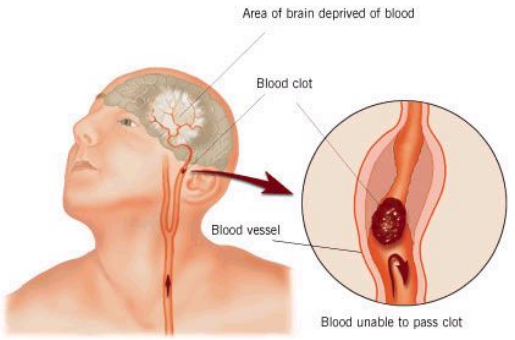
Chronic Complications of DM

A. Macrovascular Complications:

B. Microvascular Complications:

Macro-vascular Complications:

- Ischemic heart diseases.
- Cerebrovascular diseases.
- Peripheral vascular diseases.



Diabetic patients have a 2 to 6 times higher risk for development of these complications than the general population

Macro-vascular Complications:

- **Accelerated atherosclerosis** involving the aorta and large- and medium-sized arteries.
- **Myocardial infarction**, caused by atherosclerosis of the coronary arteries, is the most common cause of death in diabetics.
- **Gangrene of the lower extremities.**
- **Hypertension** due to Hyaline arteriolosclerosis.

Hypertension in DM

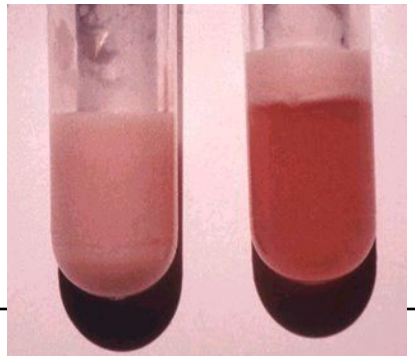
Type 1

- present after several years of DM
- affects about 30% of patients.
- Secondary to
- nephropathy
- Activation of the Renin angiotensin system

Type 2

- Mostly present at diagnosis
- Affects about 60% of patients
- Secondary to insulin resistance
- Activation of the sympathetic nervous system

Dyslipidaemia in DM



- Most common abnormality is ↓ HDL and ↑ Triglycerides
- A low HDL is the most constant predictor of Cardiovascular disease in DM.

Screening for Macrovascular Complications

1. Examine pulses for cardiovascular diseases.
2. Lipogram (lipid profile).
3. ECG.
4. Blood pressure.

Microvascular Complications

Microvascular complications are specific to diabetes and related to longstanding hyperglycaemia.

- Both Type1 DM and Type2 DM are susceptible to microvascular complications.

- The duration of diabetes and the quality of diabetic control are important determinants of microvascular abnormalities.

Pathophysiology of microvascular disease

- In diabetes, the microvasculature shows both functional and structural abnormalities.
- The structural hallmark of diabetic microangiopathy is thickening of the capillary basement membrane.
- Many chemical changes in basement membrane composition have been identified in diabetes, including increased type IV collagen and its glycosylation (i.e binding of glucose to wall of blood vessels).

- The main functional abnormalities include increased capillary permeability, viscosity, and disturbed platelet function.

- These changes occur early in the course of diabetes and precede organ failure by many years.
- Increased capillary permeability is manifested in the retina by leakage of fluorescein and in the kidney by increased urinary losses of albumin which predict eventual renal failure.

Platelets from diabetic patients show an exaggerated tendency to aggregate, perhaps mediated by altered prostaglandin metabolism.

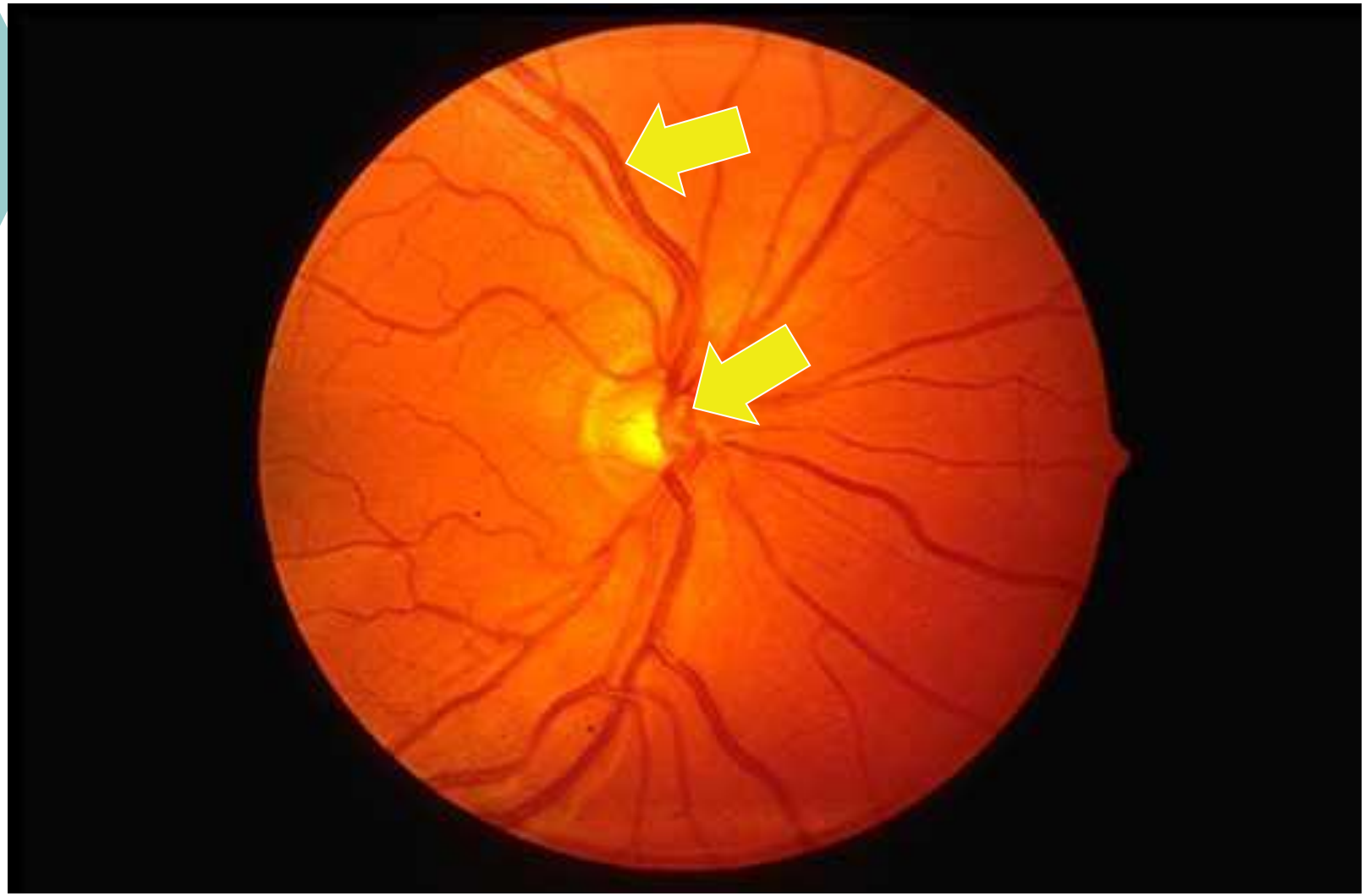
- Plasma and whole blood viscosity are increased in diabetes.
- These defects together with the platelet abnormalities may cause stasis in the microvaculature, leading to increased intravascular pressure and to tissue hypoxia.
- There is abnormal production of von Willebrand factor and endothelial derived nitric oxide by endothelial cells which could contribute to tissue damage.

1- Diabetic retinopathy

**** Pathogenesis:***

- Histologically the earliest lesion is thickening of the capillary basement membrane.
- On fluorescein angiography the first abnormality is the capillary dilatations (microaneurysms).
- Microaneurysm may give rise to haemorrhage or exudate.
- Vascular occlusion, initially of capillaries and later of arteries and veins, leads to large ischaemic areas (cotton-wool spots).

Normal Retina



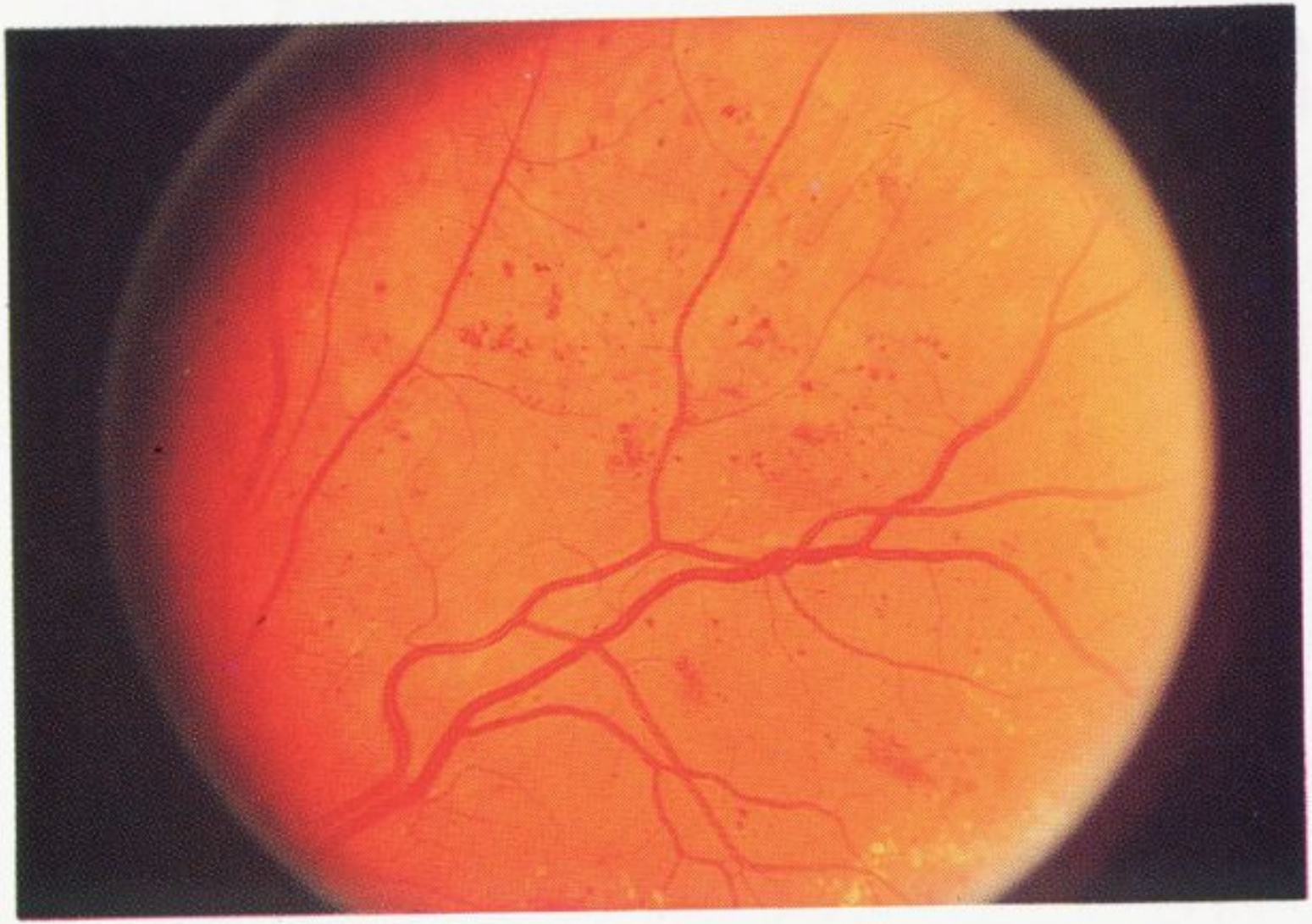
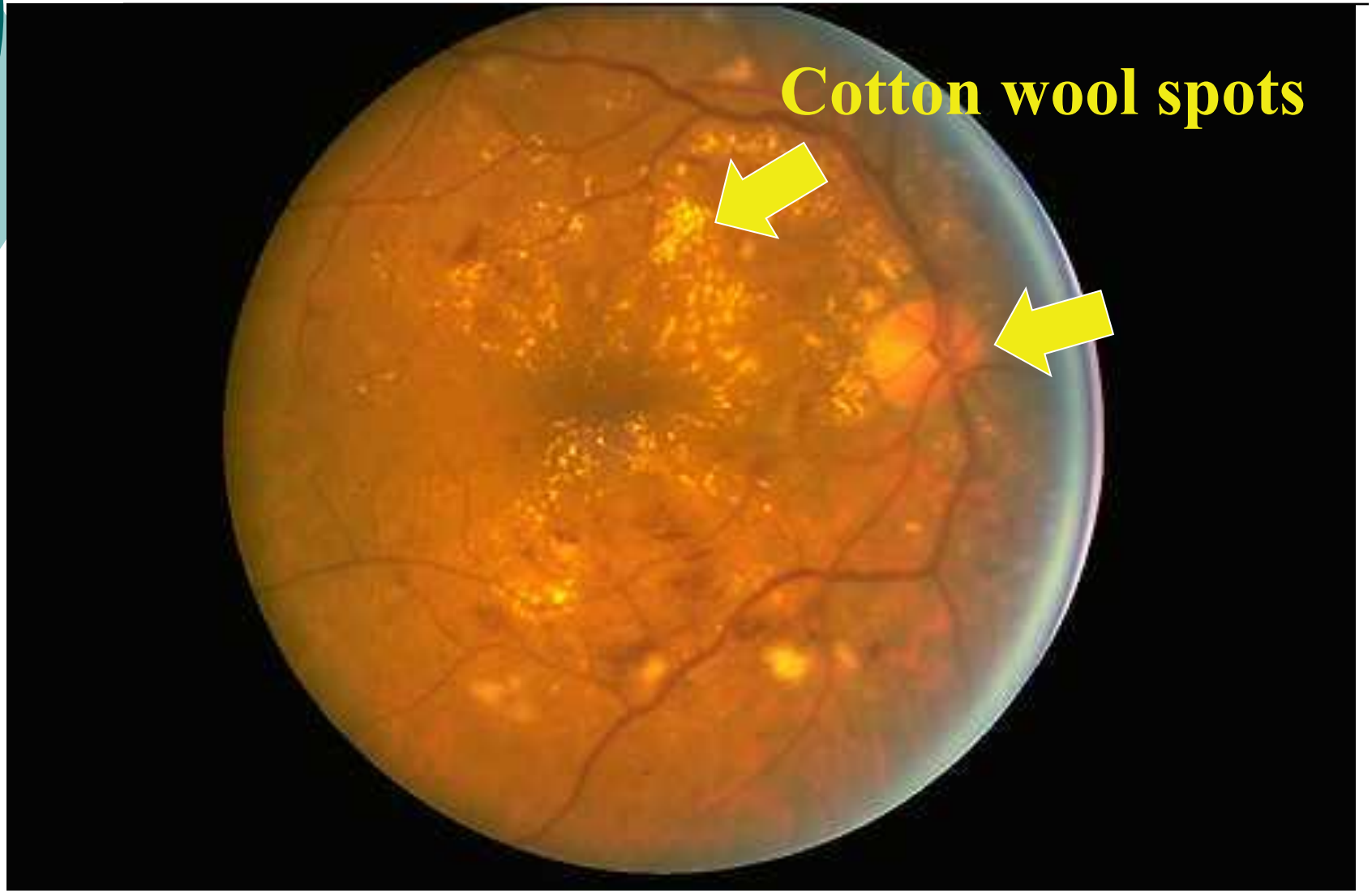


Fig. 8.1. Background diabetic retinopathy, showing scattered red 'dots and blots' (microaneurysms and haemorrhages) and exudates.

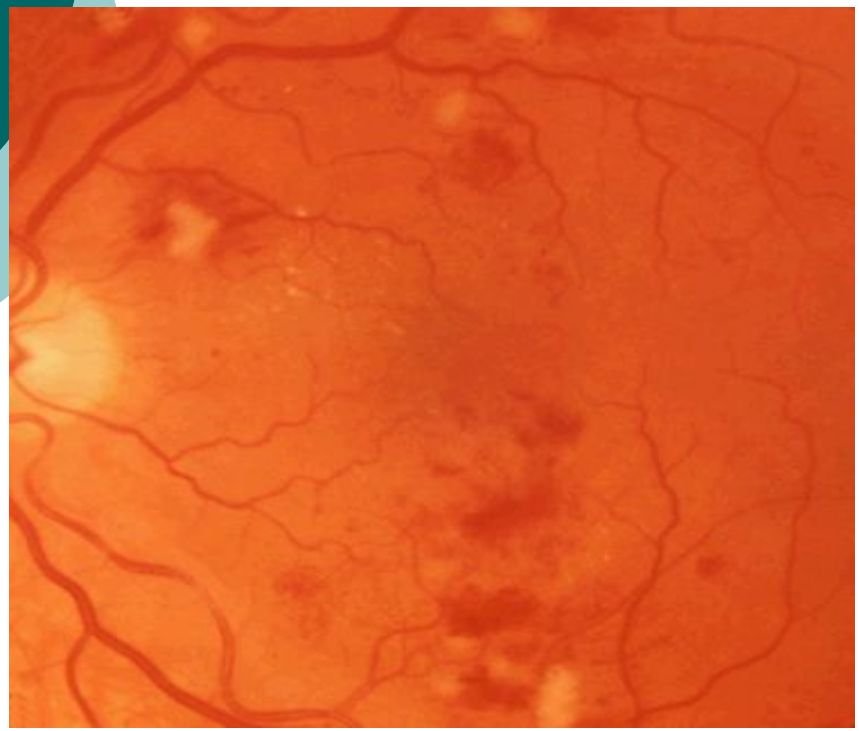
Diabetic Retinopathy

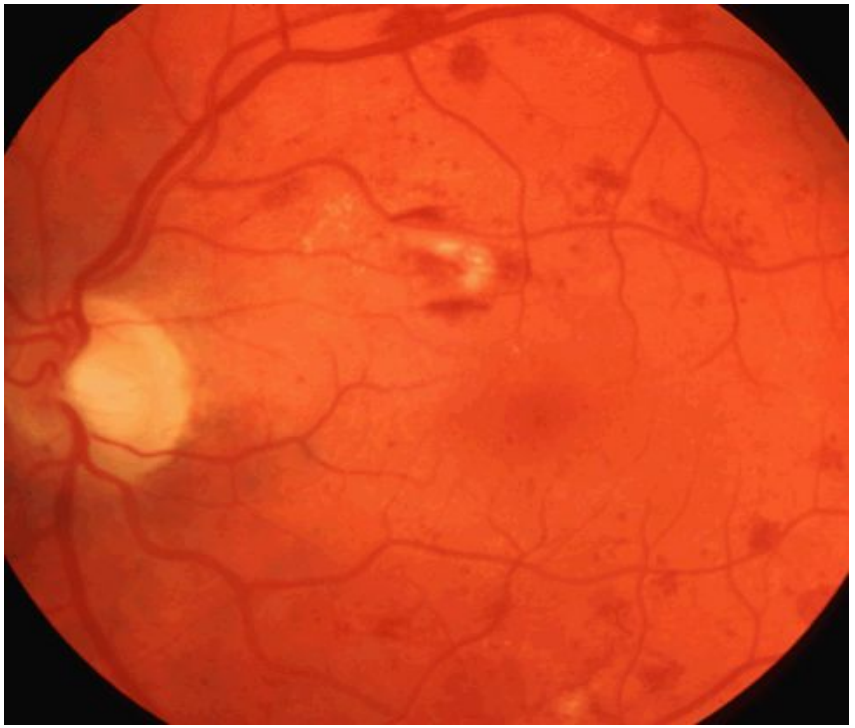


Other Eye Complications

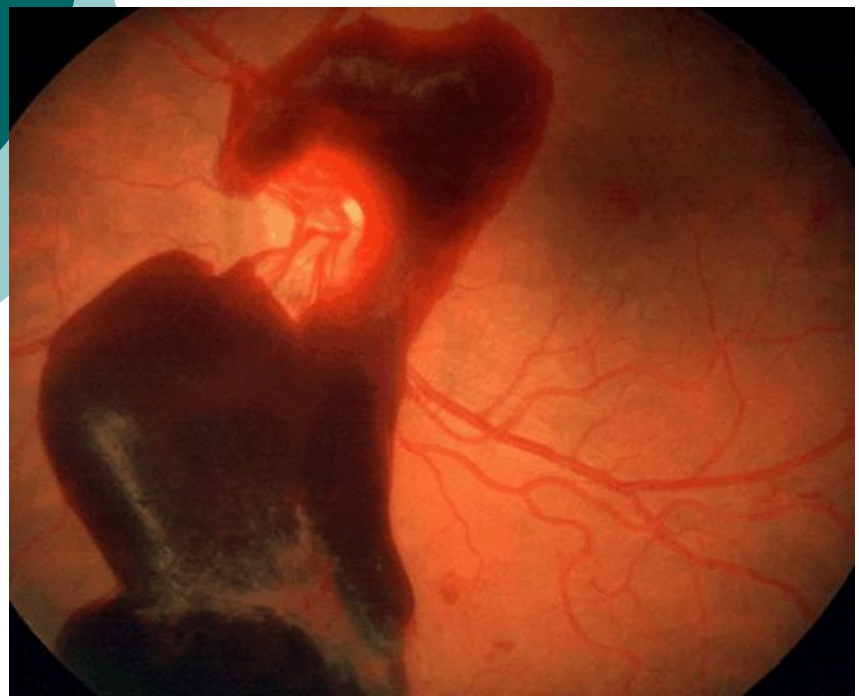
- Cataracts.
- Glaucoma
- Macular edema.
- Ischaemic maculopathy.
- Proliferative retinopathy.
- Vitreous Bleeding.
- Rubeosis Iridis

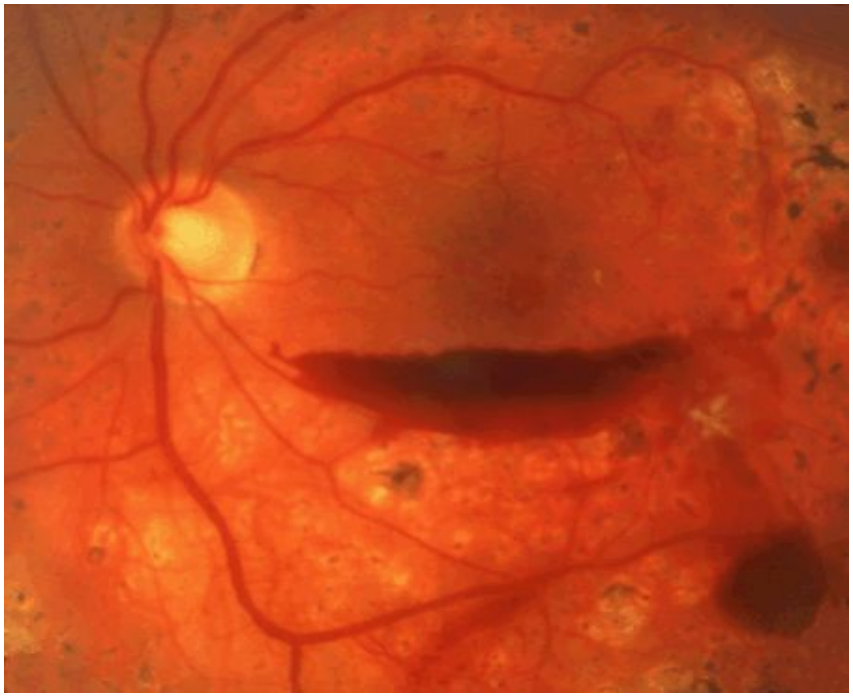
Proliferative retinopathy



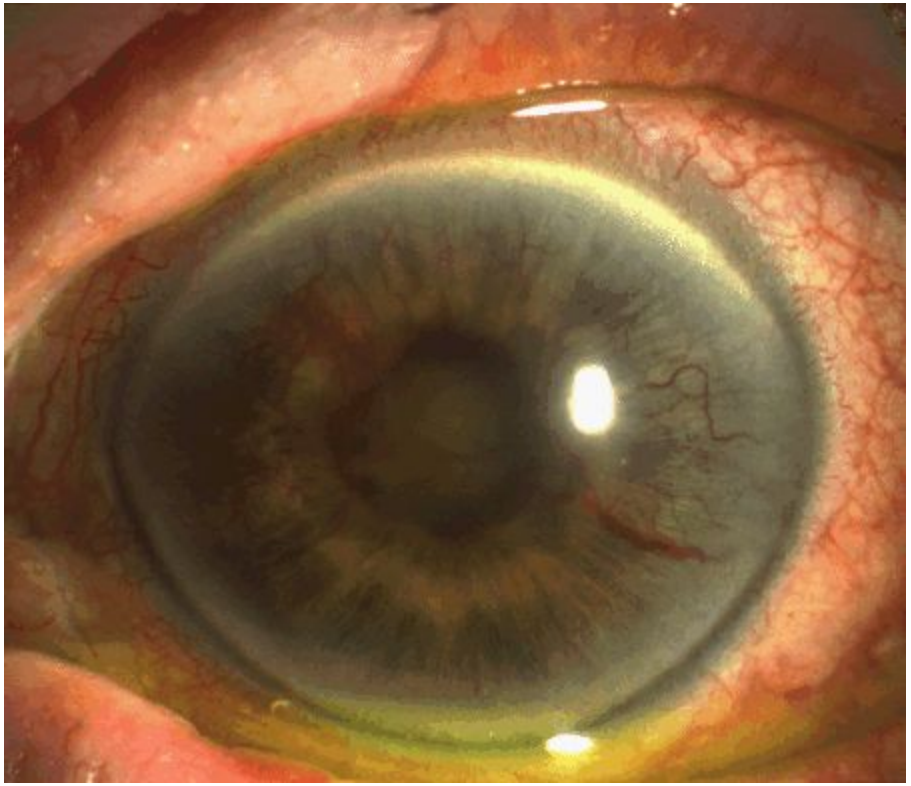


Vitreous Bleeding



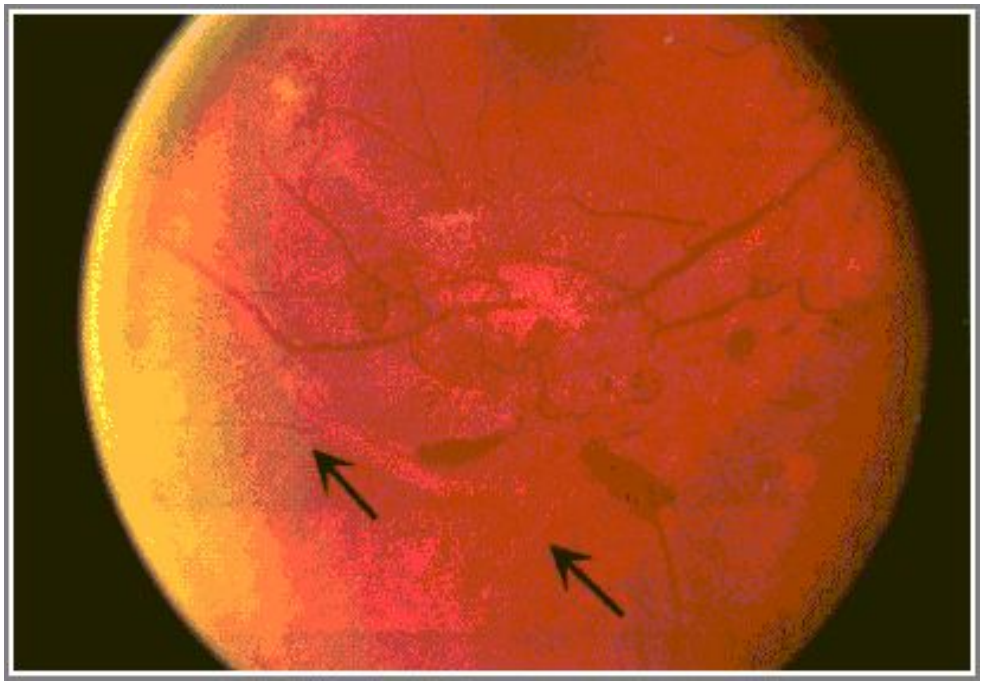


Rubeosis Iridis



Proliferative retinopathy.

- Note the abnormal capillaries and haemorrhages.



2- Diabetic Nephropathy (DN)

- Diabetic nephropathy is defined by persistent albuminuria (>300 mg/day), decrease glomerular filtration rate and rising blood pressure.

- About 20 – 30% of patients with diabetes develop diabetic nephropathy

Risk factors of DN

- Duration of DM.
- Family History of hypertension. Cardiovascular disease, nephropathy.
- Hyperglycemia.
- Hypertension.
- Microalbuminuria.
- Male gender.
- Cigarette smoking.

Pathogenesis:

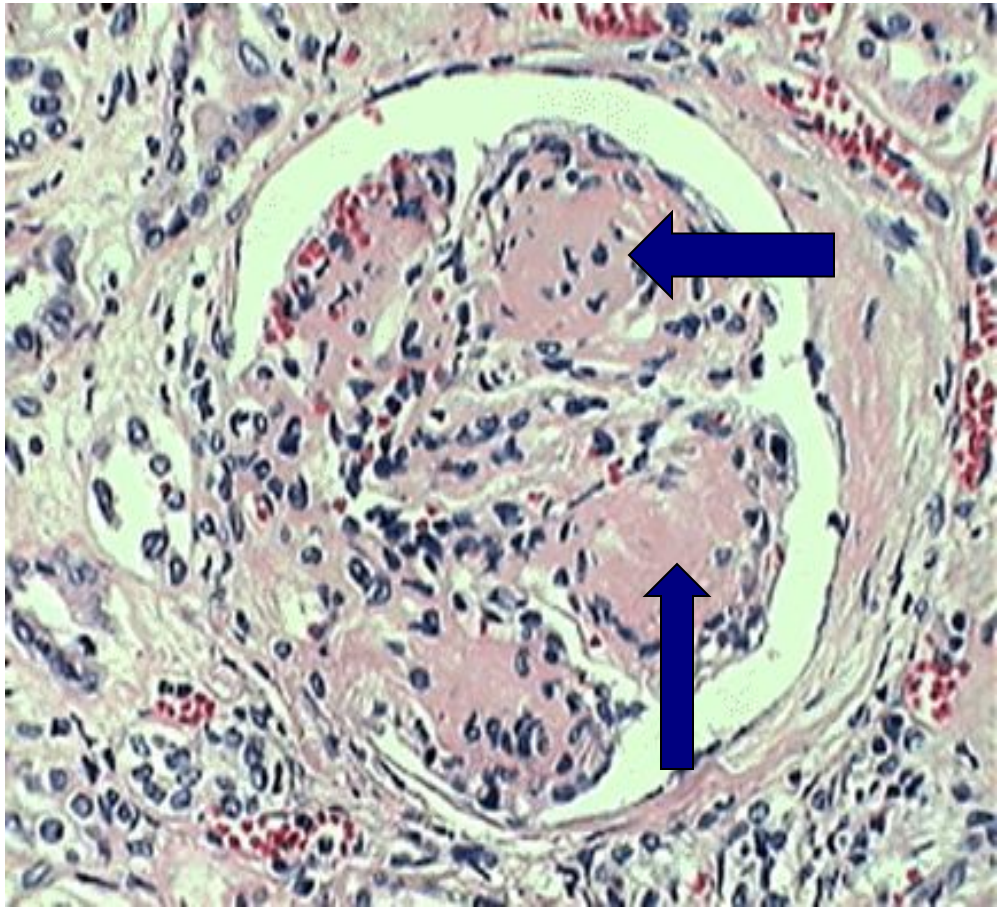
- The glomerular and vascular lesions are linked to hyperglycemia.
- Nonenzymatic glycosylation to glomerular proteins results in accumulation of irreversible advanced glycosylation end products in the glomerular mesangium and glomerular basement membrane.
- This alteration leads to proteinuria and eventually glomerulosclerosis

Pathological pattern of DN

- **Diffuse form (more common):** consist of thickining of glomerular basement membrane with generalized mesangial thickenings.
- **The nodular form (the Kimmelstiel-Wilson lesion):** (accumulation of periodic acid schiff positive material are deposit in the periphery of glomerular tufts.

Diabetic nephropathy

• The glomerulus shows sclerotic nodules in the center of the lobules or segments.



Treatment to prevent progression to DN

- Glycaemic control.
- ACE inhibitor .
- Blood pressure control.
- Smoking cessation.
- Proteins restriction.
- Lipid reduction.

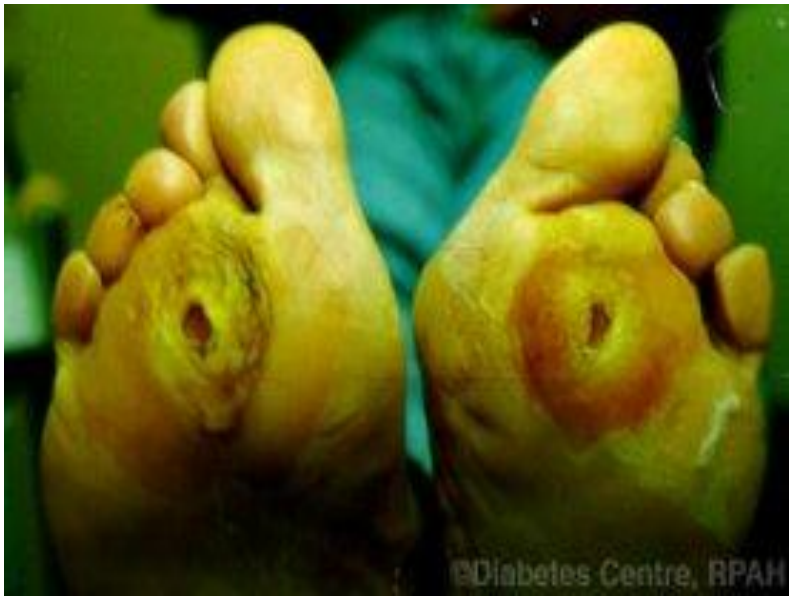
4. Diabetic Neuropathy

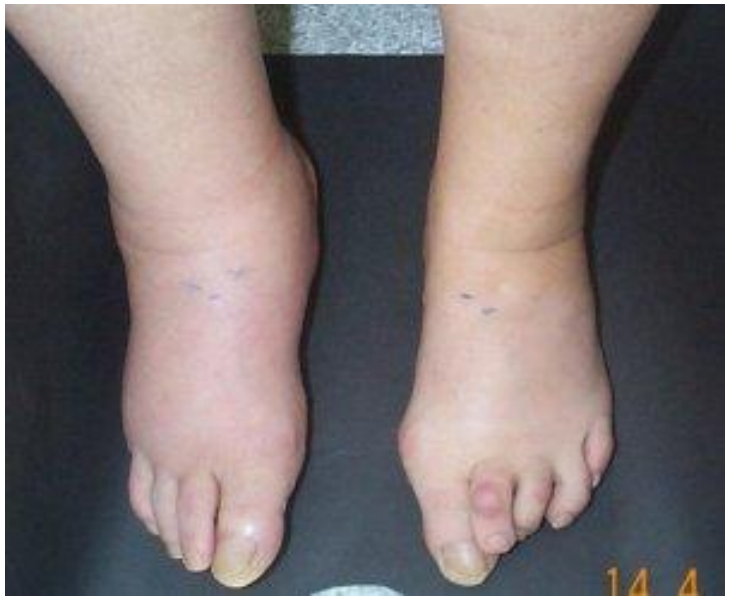
1. Sensorimotor neuropathy.
2. Autonomic neuropathy.

Sensorimotor Neuropathy

- Numbness, paresthesias.
- Feet are mostly affected, hands are seldom affected.
- Complicated by ulceration (painless), charcot arthropathy.

Complications of Sensorimotor neuropathy





Autonomic Neuropathy

- Postural hypotension.
- Diabetic diarrhea.
- Neuropathic bladder.
- Erectile dysfunction.

5. Infections

- Community acquired pneumonia
- Acute bacterial cystitis
- Acute pyelonephritis
- Pyelonephritis
- Perinephric abscess
- Fungal cystitis.

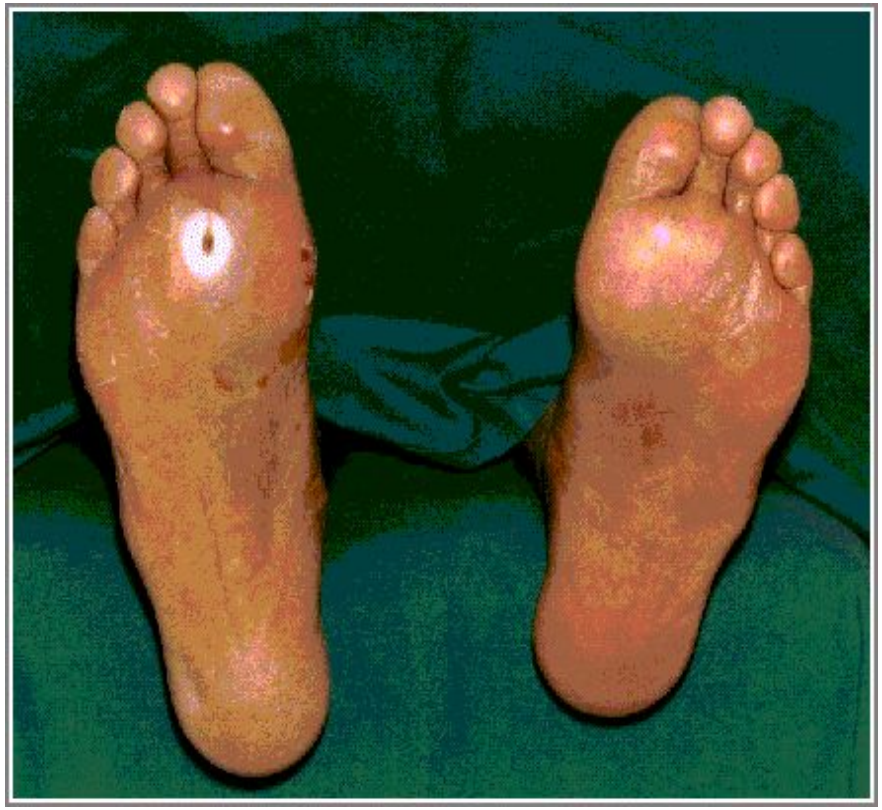
foot care

Patient should

- check feet daily
- Wash feet daily
- Keep toe nails short
- Protect feet
- Always wear shoes
- Look inside shoes before putting them on
- Always wear socks
- Break in new shoes gradually

Foot ulcer

- A foot ulcer in a diabetic patient, most probably due to nerve damage. Note the callus (hard skin) around the ulcer, indicating that the foot was subjected to excess pressure.



Diabetic Gangrene – Amp.

The end