

# Complications of diabetes mellitus

TUCOM

Dep. of Medicine

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# Complications of diabetes mellitus

## A- ACUTE COMPLICATIONS

1. Hypoglycemia
2. Diabetic Ketoacidosis
3. Non-ketotic Hyperosmolar Diabetic Syndrome or Coma
4. Lactic Acidosis

## B- CHRONIC COMPLICATIONS

### 1- Microvascular:

- Nephropathy
- Retinopathy
- Neuropathy

### 2- Macrovascular:

- Coronary artery disease
- Cerebrovascular disease
- Peripheral arterial disease

# ACUTE COMPLICATIONS

## HYPOGLYCEMIA:

**Definition:** Hypoglycemia is a clinical syndrome of diverse causes in which low levels of serum glucose can eventually lead to neuroglycopenia. Which documented by **Whipple's triad**: signs and symptoms of hypoglycemia (episodic), in the presence of a low plasma glucose concentration  $<45$  mg/dL (2.5 mmol/L), that are relieved by restoration of plasma glucose to normal concentrations.

The normal fasting plasma glucose concentration is 65-104 mg/dL (3.6- 5.8 mmol/L), but low plasma glucose values without signs and symptoms, or vice versa, do not constitute clinical hypoglycemia.

As plasma glucose levels decline just below the physiologic range, glucose counterregulatory (plasma glucose–raising) hormones are released, among these:

1. Reduce insulin secretion
2. Increase glucagon secretion (rapid response)
3. Increase epinephrine secretion (rapid response)
4. Increase cortisol and growth hormone secretion (delayed response)

Glucagon is the most important in the acute response to hypoglycemia.

In patients with type 1 diabetes of more than **5 years** duration, the **glucagon** response is lost. After **10 years** the **epinephrine** response will be lost.

# Causes of hypoglycemia

1. Hypoglycemia in diabetic patients: it is a result of treatment and not a manifestation of the disease itself. The most common cause.
2. Hypoglycemia in non-diabetic patients: it is called 'spontaneous' hypoglycemia, which have different causes and require different investigations. The rare cause.

**Note:** Hypoglycemia should be considered in all comatose patients, even if there is an apparently obvious cause, such as hemiplegic stroke or alcohol intoxication.

## **1- Causes of hypoglycemia in diabetes:**

- Missed, delayed or inadequate meal
- Unexpected or unusual exercise
- Errors in oral hypoglycemic agent (sulfonylureas, meglitinides) or insulin dose
- Lipohypertrophy at injection sites
- Gastroparesis due to autonomic neuropathy
- Malabsorption, e.g. celiac disease
- Unrecognized other endocrine disorder, e.g. Addison's disease
- Factitious (patient induced)
- Breastfeeding by diabetic mother

## **2- Causes of spontaneous hypoglycemia:**

- Alcohol
- Drugs ( $\beta$ -adrenergic blockers (nonselective), Quinine, Pentamidine, Salicylates)
- Critical illnesses ( Sepsis, Hepatic or renal failure)
- Adrenal insufficiency
- Hypopituitarism
- Insulinoma
- Non-islet cell tumour (e.g. sarcoma)
- Inborn errors of metabolism

# SIGNS AND SYMPTOMS OF HYPOGLYCEMIA

## Autonomic

Sweating  
Trembling  
Pounding heart  
Hunger  
Anxiety

## Neuroglycopenic

Confusion  
Drowsiness  
Speech difficulty  
Inability to concentrate  
Incoordination  
Irritability, anger

## Non-specific

Nausea  
Tiredness  
Headache

## Severe hypoglycaemia:

defined as any episode requiring the assistance of another person for recovery, can result in serious morbidity and has a recognized mortality of 2-4% in insulin-treated patients.





## Diagnosis of hypoglycemia:

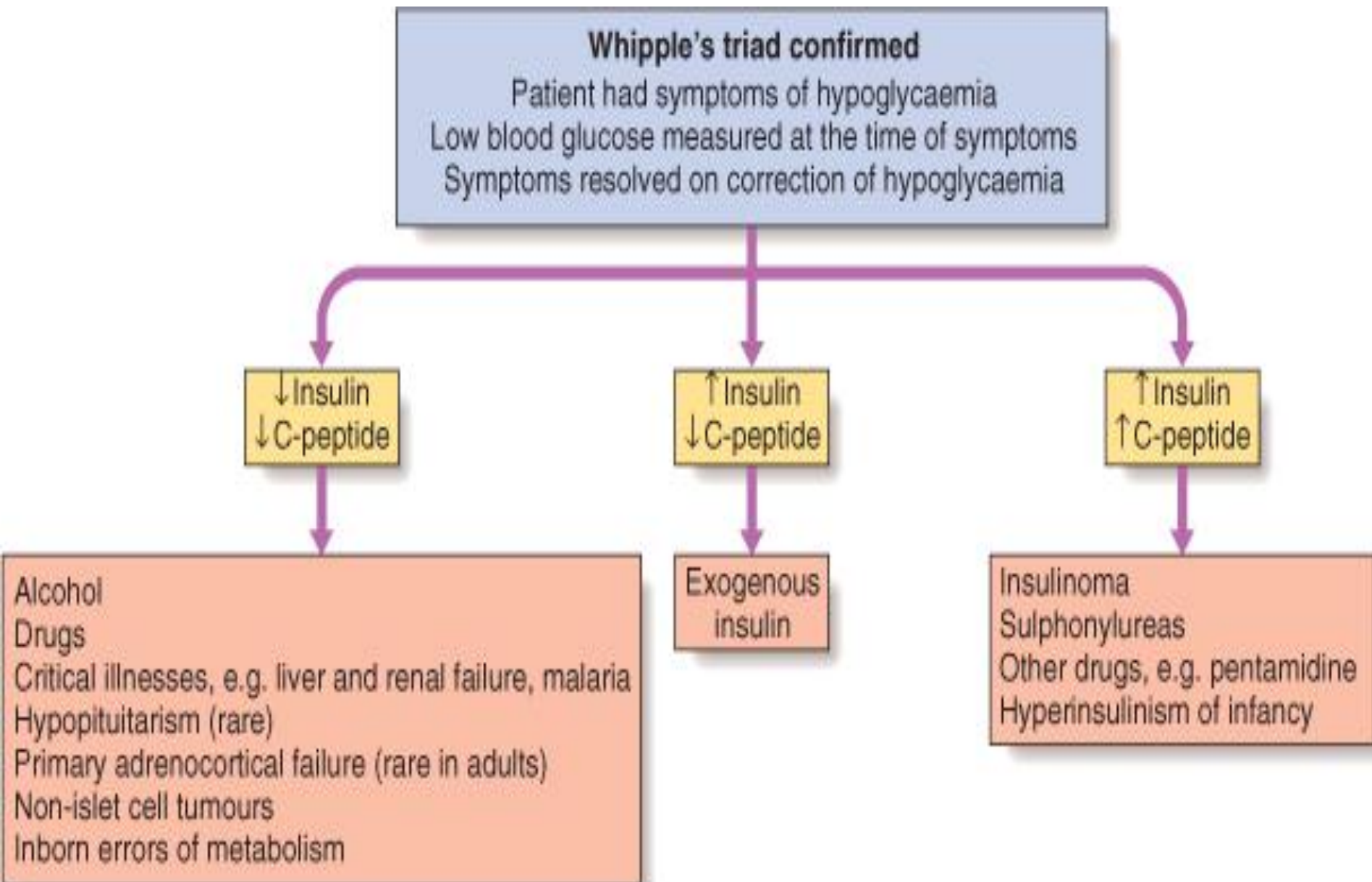
1. Clinical suspicion: in patients with typical symptoms, confusion, altered level of consciousness, seizure, or in a clinical setting in which hypoglycemia is known to occur.
2. Documentation of Whipple's triad.
3. Blood sample: to confirm hypoglycaemia and for later measurement of insulin, C-peptide, proinsulin and circulating oral hypoglycemic agents.

**Note:** Hypoglycaemia + high insulin + high C-peptide concentrations = insulinoma or sulphonylurea ingestion

# Interpretation of blood results in hypoglycemic patient

Condition	Plasma Glucose (mg/dL)	Insulin ( $\mu$ U/mL)	C-Peptide (nmol/L)	Proinsulin (pmol/L)	Plasma Sulfonylurea Level (nmol/L)
Normal	$\geq 45$	$< 6$	$< 0.2$	$< 5$	-
Insulinoma	$\leq 45$	$\geq 6$	$\geq 0.2$	$\geq 5$	-
Exogenous insulin	$\leq 45$	$\geq 6$	$< 0.2$	$< 5$	-
Sulfonylurea agents	$\leq 45$	$\geq 6$	$\geq 0.2$	$\geq 5$	$> 0.2$

# Differentiation among causes of hypoglycemia



## **Treatment of hypoglycemia:**

- If the patient is unable to swallow, intravenous glucose (30-50 ml of 20-50% dextrose) or glucagon as 1 mg by intramuscular injection (but this is ineffective in patients with depleted glycogen reserves such as liver disease).
- As soon as the patient is able to swallow, glucose should be given orally. Full recovery may not occur immediately and reversal of cognitive impairment may not be complete until 60 minutes after normoglycaemia is restored.

glucose gel given orally



**The possibility of recurrence should be anticipated in a patient using a long- or intermediate-acting insulin or a long-acting sulphonylurea and to prevent this a 10% dextrose infusion, titrated to the patient's blood glucose, may be necessary.**

**Causes of failure to regain consciousness after blood glucose is restored to normal:**

- 1. Cerebral oedema**
- 2. Alcohol intoxication**
- 3. Post-ictal state**
- 4. Cerebral haemorrhage**

# DIABETIC KETOACIDOSIS

Ketoacidosis is a major medical emergency and remains a serious cause of morbidity, principally in people with type 1 diabetes.

**The cardinal biochemical features of DKA are:**

1. *Hyperglycemia*: plasma glucose levels greater than 250 mg/dL.
2. *Ketosis*: moderate to severe ketonemia and moderate ketonuria (2+ to 3+ by the nitroprusside method)
3. *Acidosis*: pH less than or equal to 7.3 and/or bicarbonate less than or equal to 15 mEq/L



# CLINICAL FEATURES OF DIABETIC KETOACIDOSIS

## Symptoms

Polyuria

Thirst

Weight loss

Weakness

Nausea

Vomiting

Leg cramps

Blurred vision

Abdominal pain

## Signs

Dehydration

Hypotension (postural or supine)

Cold extremities

Peripheral cyanosis

Tachycardia

Air hunger (Kussmaul breathing)

Smell of acetone

Hypothermia

Confusion, drowsiness

Coma





**Dehydration**

## Investigations:

The following are important but should not delay the institution of intravenous fluid and insulin replacement:

1. Blood glucose, urea and electrolytes, plasma bicarbonate.
2. Arterial blood gases to assess the severity of acidosis.
3. Urinalysis for ketones (a semi-quantitative guide to the plasma concentration of acetoacetate and acetone).
4. ECG
5. Infection screen: full blood count, blood and urine culture, C-reactive protein, chest X-ray.

# Treatment of DKA:

The principal components of treatment are:

1. Fluid replacement
2. Administration of short-acting (soluble) insulin
3. Potassium replacement
4. Administration of antibiotics if infection is present

## Fluid replacement:

- 0.9% saline (NaCl) i.v.
  - 1 litre over 30 minutes
  - 1 litre over 1 hr
  - 1 litre over 2 hrs
  - 1 litre over next 2- 4 hrs
- When blood glucose < 15 mmol/l (270 mg/dl)
  - Switch to 5% dextrose, 1 litre 8-hourly
  - If still dehydrated, continue 0.9% saline and add 5% dextrose 1 litre per 12 hrs
- Typical requirement is 6 litres in first 24 hrs but avoid fluid overload in elderly patients
- Subsequent fluid requirement should be based on clinical response including urine output

Be more cautious with fluid replacement in elderly, young people, pregnant patients and those with renal or heart failure. If plasma sodium is > 155 mmol/L, 0.45% sodium chloride may be used.

## Insulin:

- 50 units soluble insulin in 50 ml 0.9% saline i.v. via infusion pump
  - 6 units/hr or (0.1 U/kg body weight/hr) initially
  - 3 units/hr when blood glucose is  $< 15$  mmol/l (270 mg/dl)
  - 2 units/hr if blood glucose declines to  $< 10$  mmol/l (180 mg/dl)
- Intramuscular injection (loading dose of 10-20 U followed by 5 U hourly) If an I V infusion is not possible. Or, alternatively, a fast-acting insulin analogue can be given hourly by subcutaneous injection.
- Check blood glucose hourly initially, if no reduction in first hour, rate of insulin infusion should be increased
- Aim for fall in blood glucose of 3-6 mmol/l ( $\sim 55$ -110 mg/dl) per hour. If blood glucose does not fall within 1 hour of commencing treatment, the dose of insulin should be increased until a satisfactory response is obtained.

**Potassium:** None in first litre of i.v fluid unless  $< 3.0$  mmol/l

- If plasma potassium  $< 3.5$  mmol/l, give 40 mmol added potassium
  - Give in 1 litre of fluid
  - Avoid infusion rate of  $> 20$  mmol/hr
- If plasma potassium is 3.5- 5.0 mmol/l, give 20 mmol added potassium
- If plasma potassium is  $> 5.0$  mmol/l, or patient is anuric, give no added potassium
- Catheterisation if no urine passed after 3 hrs

**Bicarbonate:** Its use is controversial. It can be used in severely acidotic patient ( $\text{pH} < 7.0$ ) . Complete correction of the acidosis should not be attempted.

**Antibiotics:** Infections must be carefully sought and vigorously treated since it may not be possible to abolish ketosis until they are controlled.

**Thromboprophylaxis:** with low molecular weight heparin

# COMPLICATIONS OF DIABETIC KETOACIDOSIS

1. **Cerebral oedema:** may be caused by very rapid reduction of blood glucose, use of hypotonic fluids and/or bicarbonate  
High mortality  
Treat with mannitol, oxygen
2. **Acute respiratory distress syndrome**
3. **Thromboembolism**
4. **Disseminated intravascular coagulation (rare)**
5. **Acute circulatory failure**

# Non-ketotic hyperosmolar diabetic syndrome or coma

This condition is characterised by:

1. Severe hyperglycaemia ( $> 50$  mmol/l (900 mg/dl))
2. Without significant hyperketonaemia or acidosis.
3. Severe dehydration and pre-renal azotemia are common.
4. Hyperosmolality ( $>350$  mosmol/L)

**Plasma osmolality =  $2(\text{Na}^+) + 2(\text{K}^+) + \text{Glucose} + \text{Urea}$  (all in mmol/L). The normal value is 280- 300 mmol/L**

It usually affects elderly patients, with type 2 DM, with a several-weeks history of polyuria, weight loss, and diminished oral intake that lead to confusion, lethargy, or coma. Physical examination reflects profound dehydration, hypotension, tachycardia, and altered mental status.

**Mortality is high (40%).**



## Treatment differs from ketoacidosis in two main respects:

- **Firstly**, these patients are usually relatively sensitive to insulin and approximately half the dose of insulin recommended for the treatment of ketoacidosis should usually be employed (3 units/hr).
- **Secondly**, the plasma osmolality is high, which may be depressed conscious level if it ( $> 340$  mmol/kg). The patient should be given 0.45% saline until the osmolality approaches normal, when isotonic (0.9%) saline should be substituted.

Thromboembolic complications are common, and prophylactic subcutaneous low molecular weight heparin is recommended.

# LACTIC ACIDOSIS

- In coma due to lactic acidosis the patient is likely to be taking metformin for type 2 diabetes.
- Patient is very ill and overbreathing but not as profoundly dehydrated.
- The patient's breath does not smell of acetone, ketonuria is absent and the plasma bicarbonate and pH are markedly reduced ( $\text{pH} < 7.2$ ).
- The diagnosis is confirmed by a high (usually  $> 5.0 \text{ mmol/l}$ ) concentration of lactic acid in the blood

## Treatment:

Intravenous sodium bicarbonate sufficient to raise the arterial pH to above 7.2, along with insulin and glucose.

Sodium dichloroacetate may be given to lower blood lactate.

The mortality in this condition is  $> 50\%$ .

# Microvascular Chronic Complications

## DIABETIC NEPHROPATHY:

Is an important cause of morbidity and mortality, and is now among the most common causes of end-stage renal failure (ESRF) in developed countries.

About 20 to 30% of diabetic patients develop nephropathy, and the incidence increases with duration of diabetes.

**Microalbuminuria:** (30 to 300 mg/24 hours) is an important indicator of risk of developing diabetic nephropathy after 10 years of type 1 diabetes and it increase the risk of macrovascular disease in patients with type 2 diabetes.

**Pathologically:** There is thickening of the glomerular basement membrane and glomerulosclerosis which either diffuse or nodular (Kimmelstiel–Wilson nodule) which is pathognomonic of diabetic nephropathy.

**Risk factors for developing diabetic nephropathy:**

- Poor control of blood glucose
- Long duration of diabetes
- Presence of other microvascular complications
- Ethnicity (e.g. Asian races, Pima Indians)
- Pre-existing hypertension
- Family history of diabetic nephropathy
- Family history of hypertension

# Management:

## ❑ Improved control of blood glucose

Treatment with metformin should be stopped when creatinine is higher than  $150 \mu\text{mol/l}$  ( $1.7 \text{ mg/dl}$ ) as the risk of lactic acidosis is increased. Long-acting sulphonylureas should be replaced by short-acting agents to decrease risk of hypoglycemia.

## ❑ Aggressive reduction of blood pressure

Institution of angiotensin-converting enzyme inhibitor (ACE-I) therapy. ACE inhibitor treatment reduced the progression to established proteinuria regardless of whether blood pressure was elevated or not.

Similar benefits from angiotensin II receptor antagonists in patients with type 2 diabetes

Non-dihydropyridine calcium antagonists (diltiazem, verapamil) may be suitable alternatives when ACE inhibitor is contraindicated.

- ❑ **Aggressive cardiovascular risk factor reduction:** with use of ACE inhibitors, statins and aspirin.
- ❑ **Renal replacement therapy:** may benefit diabetic patients at an earlier stage than other patients with ESRF.
- ❑ **Renal transplantation:** can dramatically improve the life of many.

# DIABETIC RETINOPATHY

Diabetic retinopathy is one of the most common causes of blindness in adults between 30 and 65 years of age in developed countries.

**Pathogenesis:** Hyperglycemia leads to endothelial cell proliferation, resulting in capillary closure and retinal ischemia, that leads to production of vascular endothelial growth factor (VEGF), which stimulate endothelial cell growth (causing new vessel formation).

# Type of diabetic retinopathy

## 1- Non-proliferative 'background' retinopathy:

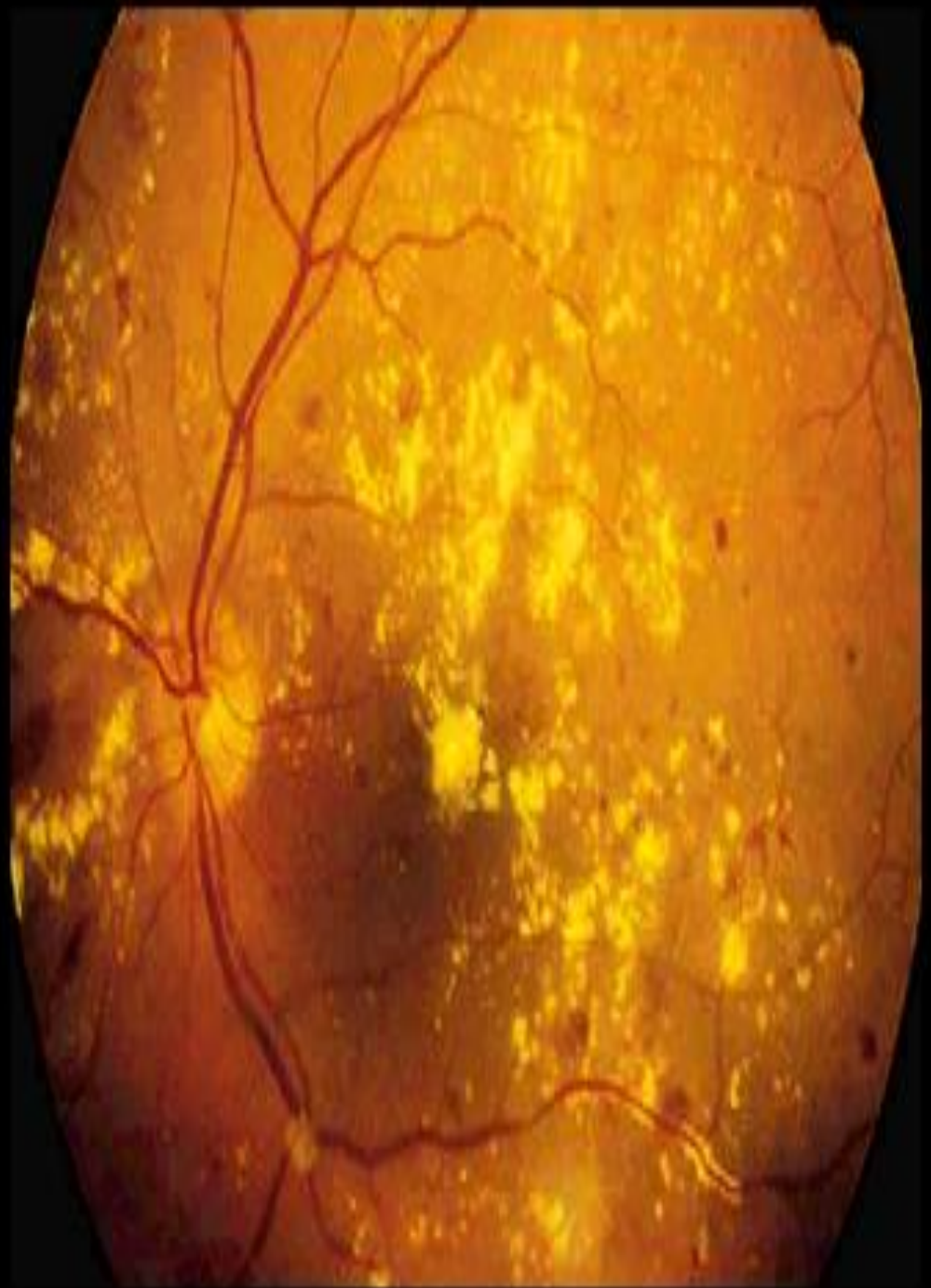
- Venous dilatation
- Peripheral  
Microaneurysms  
(dots)  
Haemorrhages  
(Blots)  
Exudates





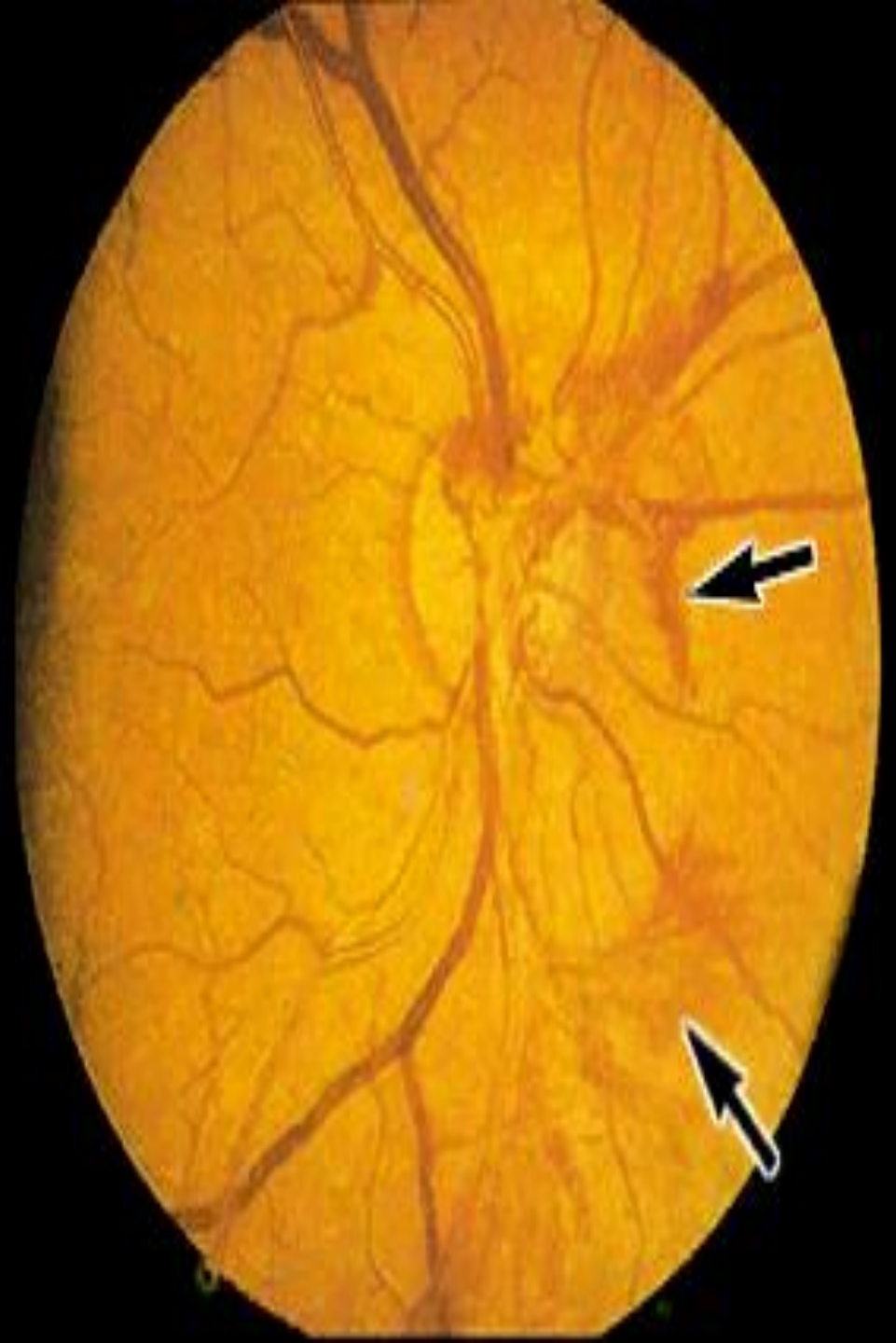
## 2- Pre-proliferative retinopathy

- Clusters/sheets of microaneurysms and small blot haemorrhages and/or large retinal haemorrhages
- Multiple cotton wool spots
- Macular oedema with Perimacular exudates



### 3- Proliferative retinopathy

- Pre-retinal haemorrhage
- Neovascularisation
- Fibrosis
- Exudative maculopathy



## **Treatment:**

- 1. Good glycaemic and blood pressure control.**
- 2. Regular screening for retinopathy is essential in all diabetic patients.**
- 3. Photocoagulation is used: to destroy areas of retinal ischaemia (since it is thought that this plays a major role in the development of neovascularisation), to seal leaking microaneurysms and to gliose new vessels directly on the retinal surface.**



# DIABETIC NEUROPATHY

This is a relatively early and common complication affecting approximately 30% of diabetic patients.

## CLASSIFICATION OF DIABETIC NEUROPATHY

### A- Somatic

#### 1- Polyneuropathy

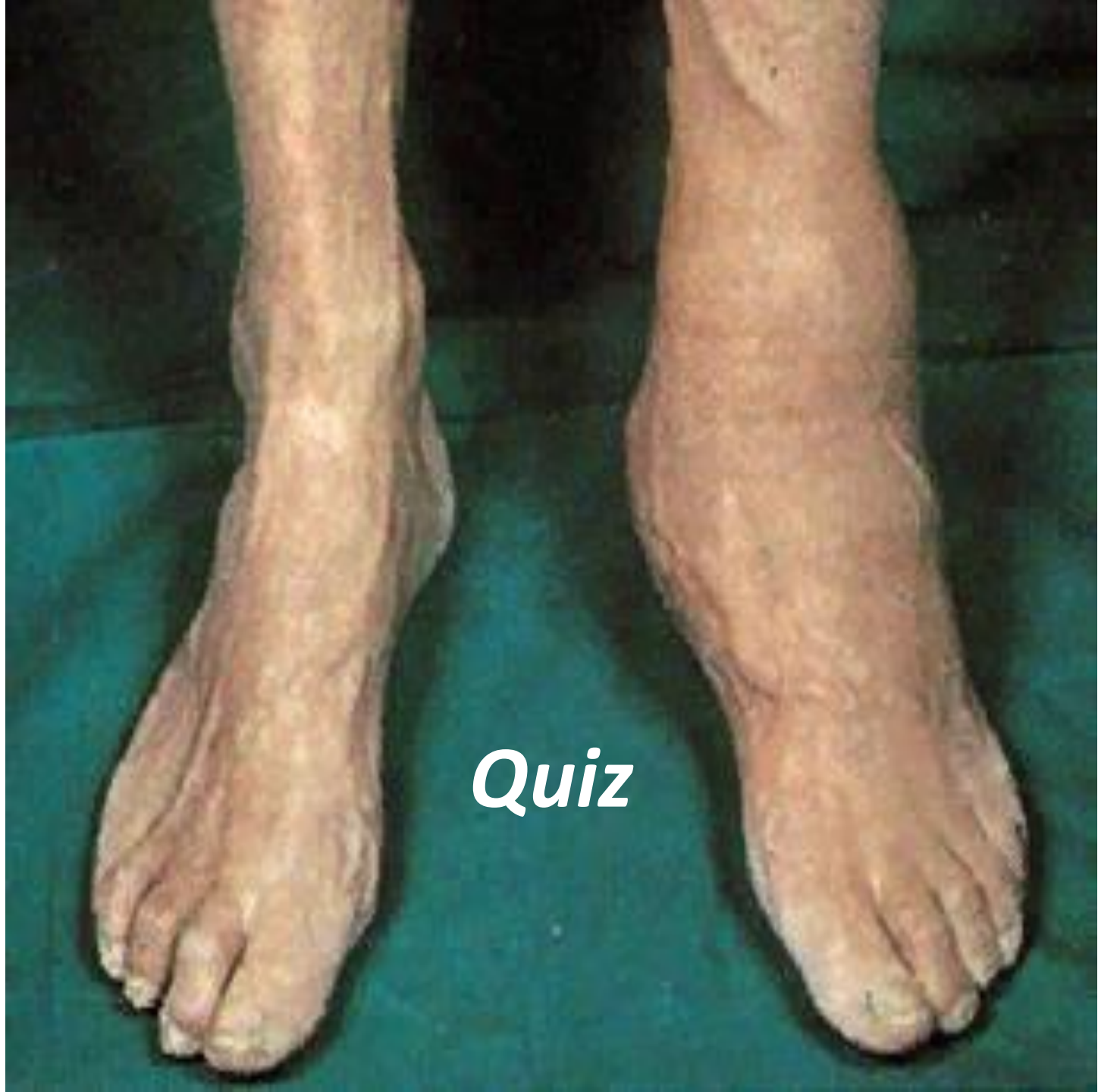
- Symmetrical, mainly sensory and distal
- Asymmetrical, mainly motor and proximal (including amyotrophy)

#### 2- Mononeuropathy (including mononeuritis multiplex)

### B- Visceral (autonomic)

- Cardiovascular
- Gastrointestinal
- Genitourinary
- Sudomotor
- Vasomotor
- Pupillary





# *Quiz*



# Quiz





**THANKS**