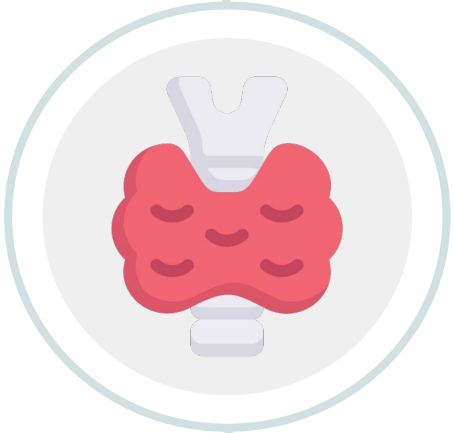
Diabetic Complications



Objectives :

- ★ Acute Diabetic Complications
  - ○ Diabetic Ketoacidosis
  - ○ Hyperglycemic Hyperosmolar State
  - ○ Hypoglycemia
- ★ Chronic Diabetic Complications
  - ○ Diabetic Retinopathy
  - ○ Diabetic Nephropathy
  - ○ Diabetic Neuropathy
  - ○ Cardiovascular Disease
- ★ How to Screen and Prevent Diabetes Complications

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Introduction

Diabetes complications

Acute	Chronic	
	Microvascular complications	Macrovascular complications
Diabetic KetoAcidosis		
Hyperglycemic Hyperosmolar State	Diabetic Retinopathy	MI
Hypoglycemia	Diabetic Nephropathy	Ischemic stroke
	Diabetic Neuropathy	Peripheral arterial disease

◀ Other Complications of Diabetes

Gastroparesis
Dental diseases
Osteoporosis
Psychological disorders
Recurrent Infections
Hearing loss
Fatty Liver Disease
more common these days

Glycated haemoglobin (HbA_{1c})

Is a measure of an individual's average blood glucose concentration over the previous 6-8 weeks. The glycation occurs as a two-step reaction,the rate at which this reaction occurs is related to the prevailing glucose concentration.**HbA_{1c}**, is expressed as a percentage of the normal haemoglobin or as the mmol concentration of HbA_{1C} per mol of normal haemoglobin (**standardized range 4-6%; 20-42 mmol/mol).**The result may be misleading if the lifespan of the red cell is altered.

◀ How to Reduce the Risk of Diabetes Complications?

- Early Diagnosis & Routine Screening Tests for complications
- Maintain a good glucose control **(A1C around 7%)**
- Maintain a good BP control **(ACEI or ARB) (< 140/90)**
- Maintain a good control of lipid (**statin**) when indicated
- Smoking cessation
- Aspirin (The use for primary prevention is controversial and recommended) only in patient with high CVD risk)
- Physical activity

Studies about diabetes complications

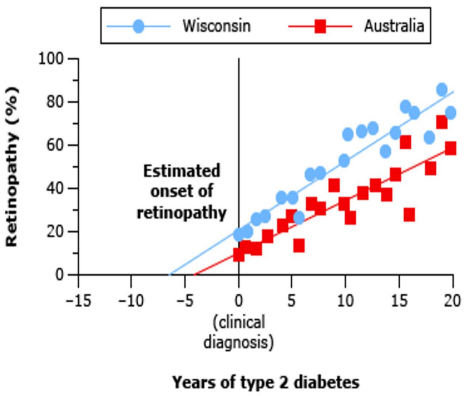
◀ UKPDS: Type 2 diabetes complications

- A study done in multiple centers in UK from 1977 – 1997
- **Does intensive glucose control reduce risk of vascular complications?**
  - Is there going to be a difference in the incidence of diabetes complications if we lower A1C down to 7% versus if we keep it at 8%?

- **Intensive glucose therapy (lowering A1C to 7%) lowered risk of:**
  - Microvascular complications by 25% (after 15 years)
  - Microalbuminuria by 33% after 12 years
  - Any diabetes-related endpoint by 12%
  - **There was a direct relationship between the glucose level and risk of vascular complications**
  - So we learned from this study that Intensive glucose control is essential in lowering the risk of diabetes complications
- **Tight Blood Pressure control (144/82 mmHg) in patients with type 2 diabetes lowered the risk of:**
  - Death by 32%
  - Stroke by 44%
  - Microvascular complications by 37%
  - Heart Failure by 56%
  - Retinopathy progression by 34%
  - Any diabetes-related endpoint by 24%

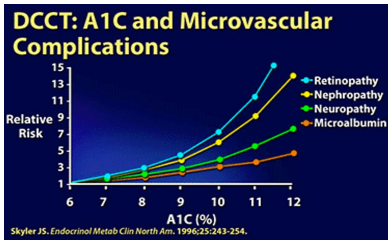
◀ Screening

- **T2D: Start screening** for complications **at time of diagnosis:** →They might have unrecognized diabetes for years thus when they are diagnosed they will have other complications(at least 10 years before diagnosis)
  - **Yearly** Dilated **Eye Exam**
  - **Yearly Albumin:**Cr ratio & Serum Creatinine[1]
  - **Yearly foot exam** (ask the patient to examine feet, routinely)
  - Other screening tests if clinically indicated
- **T1D:** (because they present early) The same but **start screening 5 years after** the time of diagnosis



◀ DCCT: Type 1 Diabetes & Complications

- Similar to UKPDS **but in patients with T1D**
- Would glucose control ameliorate the long-term complications of diabetes?



Chronic Complications of Diabetes (T1D)

1. The urine of all people with diabetes should be checked regularly for the presence of microalbuminuria. The albumin : creatinine ratio is less than 2.5mg/mmol in healthy men and less than 3.5 mg/mmol in healthy women. If microalbuminuria is detected, the test should be repeated twice because false-positive readings are common.

Diabetic Ketoacidosis

1 Diabetic Ketoacidosis (DKA):

- The 3 main features of DKA are: (metabolic) acidosis, hyperketonemia ± hyperglycemia (patients nowadays sometimes present with euglycemic DKA.
- Status of **metabolic acidosis** due to absolute (or relative) insulin deficiency in association with increased levels of glucagon and other counter-regulatory hormones resulting in **increased ketone** production.
- Mostly occurs in people with type 1 diabetes but may occasionally present in people with type 2 diabetes
- It occurs **more frequently in younger** people but the **mortality is higher in older people**

◀ Precipitating Causes of DKA

- **It is usually seen in the following circumstances:**
  - Previously undiagnosed diabetes
  - **Non compliance with insulin therapy** The most common
  - The stress of intercurrent illness and infection
  - Drugs: Corticosteroids, sympathomimetics, atypical anti-psychotics, **SGLT-2 inhibitors**(works on the PCT to enhance excretion of Na+ and glucose in the urine. as a result, the glucose and BP go down, and kidney function improves. It can induce DKA.)

Table 1 | **Precipitating causes of diabetic ketoacidosis**

Precipitating cause	Australia[115]	Brazil[116]	China[117]	Indonesia[118]	Korea[119]	Nigeria[120]	Spain[121]	Syria[122]	Taiwan[123]	USA[15,23]
New diagnosis of diabetes mellitus, %	5.7	12.2	NR	3.3	NR	NR	12.8	NR	18.2	17.2–23.8
Infection, %	28.6	25.0	39.2	58.3	25.3	32.5	33.2	47.8	31.7	14.0–16.0
Poor adherence to treatment, %	40.0	39.0	24.0	13.3	32.7	27.5	30.7	23.5	27.7	41.0–59.6
Other, %	25.7	15.0	10.9	17.1	11.2	4.8	23.3	7.8	6.2	9.7–18.0
Unknown, %	NA	8.8	25.9	8.0	30.8	34.6	NA	20.9	16.2	3.0–4.2

◀ Pathophysiology of DKA

Severe Absolute Insulin deficiency[1] & Increased glucagon

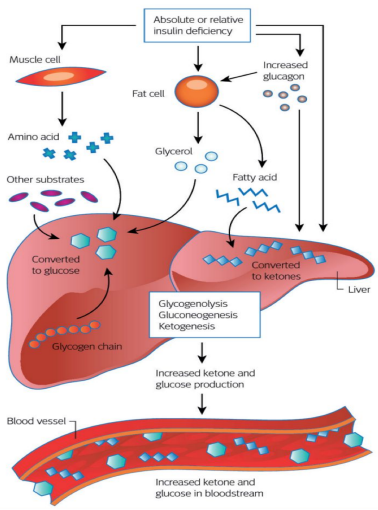
Increased activity of the **hormone-sensitive lipase** in adipose tissue

Triglycerides → glycerol & **fatty acids** (Liver) accumulate in the liver

In the liver:
Free fatty acids→ Ketones[2]

Metabolic Acidosis

- Altered mental status
- Kussmaul Breathing
- Shock



increased glucose production in the liver

Decreased glucose uptake in muscles

Hyperglycemia

Glucosuria & osmotic diuresis

- Polyuria
- Polydipsia
- Hypovolemia
- Weight loss

1. Marked insulin deficiency is a necessary precondition for DKA since very little insulin is needed to inhibit hepatic ketogenesis and the breakdown of adipose triglycerides to non-esterified fatty acids (NEFAs). Relative insulin deficiency can cause DKA but RARELY does.
2-The most important biochemical abnormality in is the **uncontrolled lipolysis** due to increased activity of hormone-sensitive lipase in adipose tissue and **uncontrolled ketogenesis** in the liver.

DKA

◀ Clinical Features of DKA

1	**Polyuria**	2	**Polydipsia**	3	**Weight loss[2]**
4	**Abdominal pain** The state of ketoacidosis leads to irritation of the peritoneum. This can cause diffuse abdominal tenderness on palpation with guarding	5	**Hypothermia [1]**	6	**change in mental status[1]**

7 **Nausea and Vomiting:**
Ketone bodies are nauseating and many people will vomit, worsening the dehydration and electrolyte loss further.

8 **Deep labored breathing (Kussmaul respiration [1]):**
- Although hyperventilation may be present, it becomes **less marked in very severe acidosis,** owing to respiratory depression.
- Hyperketonemia leads to acidosis, so the body tries to compensate by washing out CO2 (Kussmaul breathing)

9 **Dehydration [1]:**
Occurs during ketoacidosis as a **consequence of two parallel processes.**
Hyperglycemia results in osmotic diuresis, and hyperketonemia results in acidosis and vomiting.
Renal hypoperfusion then occurs and a vicious circle is established as the kidney becomes less able to compensate.

10 **Odour:**
The excess ketones are excreted in the urine but also appear in the breath, producing a distinctive smell similar to that of acetone. Smell of ketones on the breath allows an instant diagnosis to be made by those able to detect the odour.

Laboratory Findings in DKA

★ **Hyperglycemia >250mg/dL + Hyperketonemia** (or heavy ketonuria) **+High anion gap (> 12 mmol\l) metabolic acidosis<18mEq/L**

Other investigations:
- **ECG:** Cardiac rhythm should be monitored in severe DKA because of the risk of electrolyte-induced cardiac arrhythmia.
- **Infection screen:** full blood count, blood and urine culture, C-reactive protein, chest X-ray. Although leucocytosis invariably occurs in DKA, this represents a stress response and does not necessarily indicate infection.
- **Blood electrolytes should be assessed as potassium abnormalities occur frequently** (will be discussed in another slide)

Measure	DKA		
	Mild	Moderate	Severe
Plasma glucose level, mmol/l	13.9	13.9	13.9
Arterial or venous pH	7.25–7.30	7.00–7.24	<7.00
Bicarbonate level, mmol/l	15–18	10–14	<10
Urine or blood acetoacetate (nitroprusside reaction)	Positive	Positive	Positive
Urine or blood β-hydroxybutyrate, mmol/l	>3	>3	>3
Effective serum osmolality, mmol/kg*	Variable	Variable	Variable
Anion gap, mmol/l	>10	>12	>12
Alteration in sensorium	Alert	Alert or drowsy	Stupor or coma

Based on the laboratory findings you can classify the cases into : mild, moderate or severe
3 distinctive factors when it comes to classifying the severity of DKA: **pH**, **bicarb**, and **anion gap**.
pH, bicarb and anion gap correlates with the severity of DKA; however, the hyperglycemia does not.

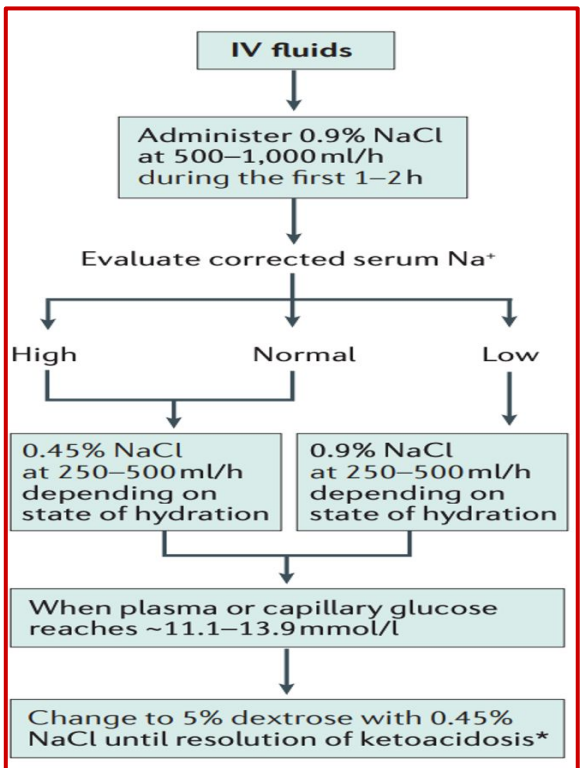
1.In severe cases
2. losing glucose in urine=losing calories

◀ Management of DKA

- **Aggressive rehydration + Lowering glucose + Cessation of ketogenesis + Correcting electrolyte imbalances.**
- Most patients with DKA are **treated in ICU**, it is associated with increased mortality.
- **The aim of treatment:**
  - lower the blood ketone concentration by 0.5 mmol/L per hour
  - increase the venous bicarbonate by 3.0 mmol/L per hour
  - reduce capillary blood glucose by 3.0 mmol/L per hour (50mg/dL per hour)
  - Maintaining potassium between 4.0 and 5.5mmol/L.

1 Rehydration

- **IV Fluid (IVF) is the most critical step.** You can give all the insulin in the world, but if the patient is not rehydrated they will remain in DKA.
- Water deficit is ~ 100ml/kg of body weight equivalent to 7.5 litres in a 75kg adult. Considered a large deficit.
- Isotonic saline (0.9% sodium chloride) at 500-1000 ml/hr during the 1st 2-4 h, Followed by isotonic saline 250—500 ml/h.
- Once the plasma glucose is **~250** mg/dl, **switch IVF to D5% IVF**. If the plasma sodium is greater than 155 mmol/L, 0.45% saline may be used initially.
- **Hartmann's solution is an acceptable alternative,**(potassium cannot added to Hartmann's solution).
- The aim of the first few litres of fluid is to correct any hypotension, replenish the intravascular deficit, and counteract the effects of the osmotic diuresis with correction of the electrolyte disturbance.
- **Over-rapid fluid** replace- may lead to **cerebral oedema**. The rate and volume of fluid replacement need to be modified in older people and in those with renal or heart failure.

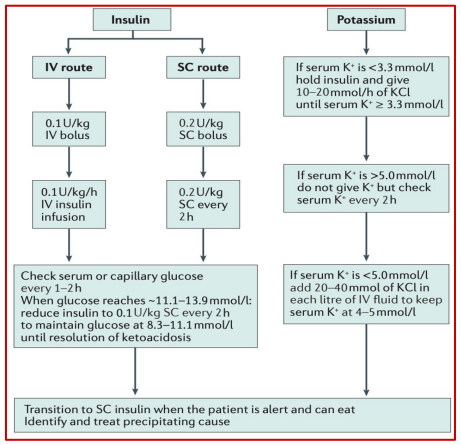


- Start with normal saline and after 1-2 hours evaluate serum NA^+
- **low**? continue with normal saline.
- **High or normal?** shift to half normal saline.
- In both cases continue IVF until the blood glucose reaches 250 mg/dL, now change to 5% dextrose with half normal saline as maintenance fluid .
- We don't want to overcorrect hyperglycemia and cause hypoglycemia.

◀ Management of DKA (cont)

2 Insulin

- **Insulin is the next step after IVF**
- **Reduces** serum glucose, **suppresses** ketogenesis, and **correct** the electrolyte disturbance.
- Another function of insulin (other than glucose level improvement) is to decrease ketone production. So, insulin is given even to patients in euglycemic DKA.
- Most of the time: we use IV insulin infusion
- Mild DKA can be treated with subcutaneous insulin (rarely)
- Most protocols: IV insulin bolus ⟶ 0.1 unit/kg/hour
- Followed by: IV insulin infusion ⟶ 0.1 unit/kg/h
- A rapid decrease in blood glucose should be avoided, as this might precipitate hypoglycaemia and the serious complication of cerebral oedema, particularly in children.
- Failure of blood glucose to fall within 1 hour of commencing
- insulin infusion should lead to a re-assessment of insulin dose.
- Should be continued until the ketosis has resolved.
- Once the person is able to eat and keep food down, subcutaneous insulin treatment should be resumed or initiated.



3 Electrolytes

- **DKA is associated with total-body K+ deficit**
- Serum **K+** is often **normal** or **high** (do not get fooled!) .
- **K+ Shift** from **intracellular** to **extracellular** compartment **with acidosis** (serum K+ looks falsely normal). Metabolic acidosis causes hyperkalemia as potassium is exchanged for hydrogen ions moving into the cell. As insulin promotes the co-transport of potassium along with glucose into cells. Although serum potassium may be elevated, there is a severe whole-body potassium deficiency as significant quantities of potassium are lost in vomit and urine. Total body K+ is decreased, but blood K+ is increased (both due to dec. insulin
- Insulin therapy moves K+ back into the cells **(watch for a drop in K+).** young people in DKA die from cardiac arrest due to hypokalemia.
    - After the initiation of treatment with insulin, potassium levels can fall rapidly. So commercially, 0.9% sodium chloride is available with premixed potassium chloride (40mmol/L (0.3%) allowing the potassium to be replaced safely.
    - We add k to the IV fluid even when serum k is normal (it should be high due to the shifting so don't miss this!) as it is not a reflection of total body k.The only time where we don't give K+ is if it is high, but once it reaches the upper limit of normal we give K+
- K+ replacement starts early (when K+ is normal), and the rate of K infusion depends on K+ level and eGFR.
- Phosphate replacement is almost never required
- Hyperchloremic acidosis may develop during treatment since a large variety of negatively charged electrolytes are lost in DKA, which are replaced with chloride.
- **AMBOSS :**
    - Potassium levels must be ≥ 3.3 mEq/L before insulin therapy is initiated
    - If potassium level is < 3.3 mEq/L, potassium should be repleted and rechecked prior to giving any insulin because Insulin causes an intracellular shift of K+, which can cause life-threatening hypokalemia.

◀ Management of DKA

4 Restoration of the acid-base balance

- **Consider bicarbonate infusion if pH <7**
- In most cases, once the circulating volume is restored, the metabolic acidosis will rapidly compensate. Bicarbonate is seldom indicated because it is implicated in the **development of cerebral oedema** and may cause a paradoxical increase in CSF acidosis.

5 Seeking the underlying cause

- Physical examination may reveal a source of infection.
- **Two common markers of infection are misleading:**
  - **fever is unusual:** even when infection is present
  - **polymorpholeucocytosis is present**: even in the absence of infection.
- Relevant investigations include a **chest X-ray, urine and blood cultures, and an electrocardiogram (to exclude myocardial infarction)**.
- If infection is suspected, broad-spectrum antibiotics are started once the appropriate cultures have been taken.

6 Other measures

- it is unlikely that they will pass urine for several hours after the initiation of fluid replacement. **However,** if no urine is passed within 2–4 hours of admission, the insertion of a urinary catheter should be considered.
- Dehydration, increased blood viscosity and coagulability of DKA increase the risk of a potentially fatal thromboembolism and so thromboprophylaxis with low-molecular-weight heparin should be considered in older or high-risk individuals unless contraindicated.

Hyperglycemic Hyperosmolar State

2 Hyperglycemic Hyperosmolar State (HHS):

- Status of **severe hyperglycemia** due to insulin resistance (not absolute insulin deficiency. For this reason, HHS typically occurs in pts with T2DM) & relative insulin deficiency resulting in **increased serum osmolality.**
- Severe hyperglycemia develops without significant ketosis, is the characteristic metabolic emergency of **uncontrolled type 2 diabetes.**
- Although typically occurring in **older patients**, HHS is increasingly seen in younger adults.
- People present in middle or later life, often with previously undiagnosed diabetes.
- Precipitating factors include consumption of glucose-rich fluids, concurrent medication such as thiazide diuretics or steroids.
- Evidence of underlying illness, such as pneumonia or pyelonephritis, may be present.

HHS

How HHS differs from DKA?

- ~ 10 times higher mortality than DKA. It's an acute complication but happens over a longer period of time because ketones aren't increased so the patient presents later
- Slower development (over several days)
- No ketosis or minimal ketosis
  - The degree of insulin deficiency is less severe. Endogenous insulin levels are sufficient to inhibit hepatic ketogenesis but insufficient to inhibit hepatic glucose production.
- Higher serum glucose level than DKA
- More severe dehydration & higher plasma osmolality than DKA
  - Old people experience thirst less acutely and become dehydrated more readily.
  - In addition, the mild renal impairment associated with age results in increased urinary losses of fluid and electrolytes.
- Gradual worsening of polydipsia, polyuria, & weight loss
- Impaired consciousness is more common than DKA

Pathophysiology of HHS

- Results from **relative** insulin deficiency (there is some detectable insulin) .
- Less activation of the hormone-sensitive lipase in adipose tissues & less free fatty acid production compared to DKA.
- No ketones production but higher serum glucose than in those with DKA.
- Severe dehydration and plasma hyperosmolality lead to impaired consciousness.

Laboratory Findings in HHS

- Severe hyperglycemia (> 30 mmol/L (600 mg/dL)
- Hyperosmolality (serum osmolality >320 mOsmol/kg)
- Without significant ketonaemia (<3 mmol/L) or acidosis (pH >7.3 (H+ <50 nmol/L), bicarbonate >15 mmol/L)
- Glycosuria, leading to an osmotic diuresis with loss of water, sodium, potassium and other electrolytes
- Hypovolemia
- Why is the pH high? the metabolic alkalosis is due to hypovolemia (contraction alkalosis/metabolic alkalosis)

Measure	DKA			HSS
	Mild	Moderate	Severe	
Plasma glucose level, mmol/l	13.9	13.9	13.9	33.3
Arterial or venous pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Bicarbonate level, mmol/l	15–18	10–14	<10	>15
Urine or blood acetoacetate (nitroprusside reaction)	Positive	Positive	Positive	Negative or low positive
Urine or blood β-hydroxybutyrate, mmol/l	>3	>3	>3	<3
Effective serum osmolality, mmol/kg*	Variable	Variable	Variable	>320
Anion gap, mmol/l	>10	>12	>12	<12
Alteration in sensorium	Alert	Alert or drowsy	Stupor or coma	Stupor or coma

HHS

◀ Management of HHS

- Management of HHS is similar to that of DKA
- The aims are to normalise osmolality, replace fluid and electrolyte losses, and normalise blood glucose, at the same time as preventing complications such as arterial or venous thrombosis, cerebral oedema and central pontine demyelinosis.
- Historically management of HHS has followed DKA guidelines, but increasing recognition of the differences between HHS and DKA has led to new approaches in HHS.
- The most important aspect of management is **fluid replacement; 0.9% sodium chloride is the treatment of choice**, but 0.45% sodium chloride may be considered if the osmolality is not declining despite adequate fluid balance.
- The rate of fall of plasma sodium should not exceed 10mmol/L in 24 hours because the resultant change in osmolality may cause cerebral damage.
- Fluid replacement is often enough to lower the glucose but insulin (0.05 units/kg per hour) should be used if the glucose is no longer falling with fluids alone or if the patient develops significant ketonaemia, when the diagnosis should be reconsidered.
- **In order to prevent cerebral damage**, the fall in blood glucose should be no more than 5 mmol/L per hour (90 mg/dL per hour)
- Prophylactic low-molecular-weight heparin should be given.

Hypoglycemia

3 Hypoglycemia:

- **Plasma glucose <3.9 mmol/L (<70 mg/dl)** this is for patients with diabetes. in normal people the cutoff is less than 54 g/dl
- **Severe hypoglycemia: need for assistance from another person to correct glucose**
- **Most frequent & serious adverse effect of glucose-lowering therapies**
- **What is the most common adverse effect of insulin therapy ? Hypoglycemia.**
- Mainly due to **Insulin** & less frequently **sulfonylureas**.
- Uncommon in people without diabetes but relatively frequent in people with diabetes
- Hypoglycemia in a patient with diabetes is almost always due to glucose-lowering therapies
- Major barrier to achieving desirable glucose control
- Occurs in 30-40% of patients with T1DM
- Occurs in 10-30% of patients with insulin-treated T2D

Hypoglycemia

◀ Clinical features

- Symptoms of hypoglycaemia are idiosyncratic, differing with age and duration of diabetes,and also depending on the circumstances in which hypoglycemia occurs.
- They comprise two main group:
  - those related to acute **activation of the autonomic nervous system** :
    - ❑ **Increased sympathetic activity:** tremor, pallor, anxiety, tachycardia, sweating, and palpitations
    - ❑ **Increased parasympathetic activity:** hunger, paresthesias, nausea, and vomiting.
  - those secondary to glucose deprivation of the brain **(neuroglycopenia).**
- Hypoglycemia also affects mood, inducing a state of increased tension and low energy.

i 20.18 Most common symptoms of hypoglycaemia

Autonomic	
• Sweating	• Hunger
• Trembling	• Anxiety
• Pounding heart	
Neuroglycopenic	
• Delirium	• Inability to concentrate
• Drowsiness	• Incoordination
• Speech difficulty	• Irritability, anger
Non-specific	
• Nausea	• Headache
• Tiredness	

N.B. Symptoms differ with age; children exhibit behavioural changes (such as naughtiness or irritability), while older people experience more prominent neurological symptoms (such as visual disturbance and ataxia).

Factors contributing to hypoglycaemia

- Insufficient patient education.
- Medications (insulin , sulfonylureas , glinides , quinolones).
- Aggressive treatment protocols targeting normoglycaemia.
- Poor coordination of insulin administration and food delivery.
- Abrupt changes in nutritional intake
- Abrupt discontinuation of parenteral or enteral nutrition among insulin - treated patients.
- Decline in renal or hepatic function
- Severe illness
- Tapering of steroid doses without appropriate reductions in insulin
- Inappropriate insulin dosing
- Counter - regulatory hormone deficiencies
- Impaired awareness of hypoglycaemia
- Dementia
- Age > 65 years
- Sepsis

◀ Treatment: (Rule of 15) ★

Give 15 grams of carbohydrates

- ➢ 4 glucose tablets
- ➢ ½ cup of fruit juice or regular soda
- ➢ 1 tablespoon of sugar or honey

Wait 15 minutes and re-check glucose

Repeat the same if glucose is still less than 70 mg/dl

If glucose is above 70 mg/dl, have the patient eat a regular meal or a snack that **contains protein** (e.g. nuts, cheese, chicken, meat, etc)

Oral carbohydrate usually suffices if hypoglycemia is recognised early. If parenteral therapy is required, then as soon as the patient is able to swallow, glucose should be given orally.

Remember, the patient **should not be driving** with hypoglycemia or (within 1 hour after treating hypoglycemia)

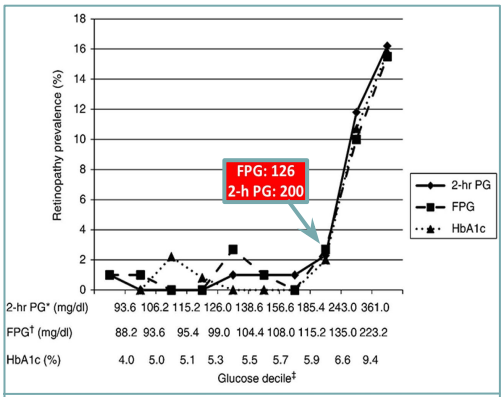
Chronic Diabetic Complications

- **Micro-:** Retinopathy, Neuropathy, and Nephropathy.
- **Macro-:** Ischemic Heart Disease (IHD),Cerebrovascular events, Peripheral Vascular Disease (PVD)
- **Mortality**

★ Complications of Type 2 Diabetes:

- **Diabetes is the leading cause of:**
  - Blindness
  - Renal failure
  - Non-traumatic lower extremity amputation
- The presence of DM complication tremendously increases medical care cost
- Usually present after long period of hyperglycemia
- Fortunately, they can be delayed/prevented by early DM detection and better glucose control

The definition of Diabetes is based on risk of Retinopathy



- The cutoffs for the diagnosis of DM are based on the risk of retinopathy
- To reduce the risk of complications, you should improve your glycemic control

Diabetic retinopathy

1 Retinopathy:

- Most commonly diagnosed diabetes-related complication, prevalence increases with the duration of diabetes
- Approximately 20% of people with type 1 diabetes will have retinal changes after 10 years, rising to 90% after 20 years ; 20–30% of people with type 2 diabetes have retinopathy at diagnosis.

Non-proliferative (earliest change)	• Usually appears in the 1st decade of the disease or early 2nd decade. • Characterized by **retinal vascular microaneurysms**, **blot hemorrhage**, and **cotton-wool spots**
Proliferative	• **Hypoxemia** & **neovascularization** leading to **virtuous hemorrhage**, fibrosis, and retinal detachment • Some of these new vessels are inside the retina and give the appearance of intraretinal microvascular abnormalities (IRMAs), sometimes vessels induced to grow on the pupil margin (rubeosis) and give rise to a rapid increase in intraocular pressure (rubeotic glaucoma).
Macular edema	• can occur in non proliferative or proliferative stage. The most common cause of visual loss.

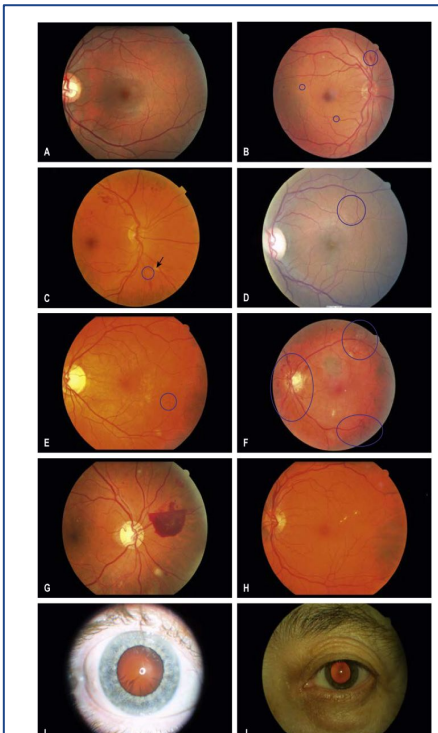


Fig. 23.14 Features of diabetic eye disease. **(A)** The normal macula (centre) and optic disc (to left). **(B)** Microaneurysms (small circles) and blot haemorrhage (larger circle) – early non-proliferative retinopathy. **(C)** Hard exudates (circled) and single cotton wool spot (arrowed) in addition to multiple blot haemorrhages in non-proliferative retinopathy. **(D)** Intraretinal microvascular abnormalities (IRMA) – pre-proliferative retinopathy (circled). **(E)** Venous loop (circled) also indicates pre-proliferative change. **(F)** Fronds of new vessels on the disc and elsewhere (proliferative; circled). **(G)** Pre-retinal haemorrhage in proliferative disease. **(H)** Hard exudates within a disc-width of the macula (maculopathy). **(I)** Cortical cataracts and **(J)** central cataracts can be seen against the red reflex with the ophthalmoscope.

Retinopathy

◀ Other ways in which DM can affect the eye:

- **Cataract:** caused by the denaturation of the protein and other components of the lens of the eye, which renders it opaque.
- **Refractory defects:** result of osmotic changes within the lens (the absorption of water into the lens causes temporary hypermetropia). This presents as fluctuating difficulty in reading but people should be reassured that this resolves with better metabolic control of the diabetes.
- **External ocular palsies**
- **Glaucoma:** open angle glaucoma
- **Blindness**

◀ Treatment of Diabetic Retinopathy

Treatment of Diabetic Retinopathy
• **Prevention** (most effective treatment) easier than treating.
• **Glycemic** & **BP** control will slow the progression
• Laser Photocoagulation
• Ocular injection (Anti-VEGF therapy for macular edema)
• Yearly Screening (Dilated Eye Exam) for all patients. You start screening 5 years after dx of T1DM. You screen at the time of dx for T2DM
laser photocoagulation: • To treat new vessels of proliferative retinopathy. • Although laser treatment prevents blindness, the main adverse effects result from the destruction of retinal tissue. The visual field becomes permanently smaller and there is reduced dark adaptation. In essence, peripheral vision is sacrificed to maintain central vision.
Vitreoretinal surgery: • used if bleeding is recurrent and preventing laser therapy. • It is also employed to try to salvage some vision if an intravitreal haemorrhage fails to clear and to treat fibrotic traction retinal detachment in advanced retinopathy.
ocular injection (intravitreal injection): • Repeated injections of anti-VEGF drugs, such as bevacizumab, aflibercept and ranibizumab. • therapy for macular edema, can control proliferative diabetic retinopathy and sight-threatening maculopathy.

Diabetic nephropathy

2 Nephropathy:

- Characterized by gradually increasing urinary albumin excretion and blood pressure as the glomerular filtration rate falls insidiously towards end-stage renal disease. Glomerular hyperfiltration → microalbuminuria→ macroproteinuria→ progression to CKD.
- Always think about the other risk factors e.g HTN.
- **Patients with diabetic nephropathy, almost ALWAYS, have evidence of diabetic retinopathy**
- **If your patient with diabetes has nephropathy but no retinopathy; it is very likely that the nephropathy is NOT due to diabetes.**
- Manifests 15–25 years after the diagnosis of diabetes but affects 25–35% of people diagnosed under the age of 30 years. It is the leading cause of premature death in young people with diabetes.
- **Other ways in which DM can damage the kidney:**
  - ischaemic lesion: Arteriolar lesions, with hypertrophy and hyalinization of the vessels, can occur
  - urinary tract infection: more common in women with diabetes, but not in men.

◀ Investigations

- **Screen with Urinary high Albumin: Creatinine &/or low eGFR.**
- The urine of all people with diabetes **should be checked regularly (at least annually)** for the presence of microalbuminuria.
- **Albuminuria** (Albumin: **Cr >30 mg/g**). is the earliest clinical sign of diabetic nephropathy. The extent of albuminuria correlates with the risk of cardiovascular disease.
- **Once proteinuria is present**, other possible causes should be considered, but once these are excluded, a presumptive diagnosis of diabetic nephropathy can be made.
- **Clinical suspicion of a non- diabetic cause** of nephropathy may be provoked by an atypical history, the absence of diabetic retinopathy and the presence of red-cell casts in the urine. Diabetic nephropathy is usually preceded by diabetic retinopathy, so if someone presents with nephropathy only, it is likely due to another cause (it could still be DM but you have to rule out other causes first).
- **Renal biopsy (Kimmelstiel-Wilson nodules)** should be considered in such cases but is rarely necessary or helpful.
- Plasma creatinine level and eGFR should be measured regularly.

Treatment of Diabetic Nephropathy
• Prevention (most effective treatment).
• Aim is to slow the disease progression (or reverse it)
• Glucose & BP (target BP <130/80 mmHg) control is key.
• **ACEI (or ARBs) are recommended to treat nephropathy**. Prevent the progression of albuminuria and may protect against renal tubulointerstitial fibrosis.
• SGLT-2 inhibitors can be used, decrease the risk and progression of diabetic nephropathy.
• Remember to change doses (or stop) medications that are renally cleared if eGFR is low • Oral antidiabetes agents, partially excreted via the kidney (e.g. glibenclamide and metformin), should be avoided. • As insulin clearance is reduced in advanced renal disease, insulin dosage is usually reduced.
• ESRD management: chronic ambulatory peritoneal dialysis may be preferable to haemodialysis, The failure rate of renal transplants is somewhat higher than in people without diabetes.

Diabetic neuropathy

3 Neuropathy:

★ **Treat with preventive foot care**

Polyneuropathy

- Most common form is **distal symmetric polyneuropathy.**
- Usually affects sensory nerves in a "stocking/glove pattern"—Typically begins in feet, later involves hands (longest nerves affected first).
- Tingling, numbness
- loss of sensation leads to the following: ulcer formation (patients do not shift their weight) with subsequent ischemia of pressure point areas; **Charcot joints.**
- Loss of fine touch, proprioception, and vibration. Loss of ankle deep reflex
- **Painful diabetic neuropathy**—hypersensitivity to light touch; severe "burning" pain, especially at night, that can be difficult to tolerate. Treatment is with gabapentin, tricyclic antidepressants, or pregabalin.

Mononeuropathies

- Dysfunction of cranial or peripheral nerves
- less common
- Most often involves **CN III**, but may also involve CN VI and IV.
- **Diabetic third nerve palsy:** eye pain, diplopia, ptosis, inability to adduct the eye; but the pupils are spared.
- Median nerve neuropathy, ulnar neuropathy, common peroneal neuropathy.
- Diabetic lumbosacral plexopathy—severe, deep pain in the thigh; atrophy and weakness in thigh and hip muscles; recovery takes weeks to months.
- Diabetic truncal neuropathy—pain in distribution of one of the intercostal nerves.

Autonomic neuropathy

- **Impotence in men** (most common presentation)
- Neurogenic bladder—retention, incontinence
- **Gastroparesis**—chronic nausea and vomiting, early satiety. **Give metoclopramide or erythromycin**
- Constipation and diarrhea (alternating)
- Postural hypotension

Summary

Diabetic ketoacidosis

Pathogenesis: Status of **metabolic acidosis** due to absolute (or relative) insulin deficiency in association with increased levels of glucagon and other counter-regulatory hormones resulting in **increased ketone** production.
Clinical features: polyuria , polydipsia , nausea , vomiting,weight loss, hypothermia, change in mental status, dehydration, Kussmaul respiration
Investigations: Hyperglycemia >250mg/dL + Hyperketonemia (or heavy ketonuria) +High anion gap (> 12 mmol\l) metabolic acidosis<18mEq/L
Management: Aggressive rehydration + Lowering glucose + Cessation of ketogenesis + Correcting electrolyte imbalances.

Hyperglycemic hyperosmolar state

Pathogenesis: Status of **severe hyperglycemia** due to insulin resistance (not absolute insulin deficiency) & relative insulin deficiency resulting in **increased serum osmolality. without ketone body production**
Clinical features: Gradual worsening of polydipsia, polyuria, & weight loss , impaired consciousness
Investigation: Severe hyperglycemia (> 30 mmol/L (600 mg/dL) , Hyperosmolality (serum osmolality >320 mOsmol/kg) Without significant ketonaemia (<3 mmol/L) or acidosis (pH >7.3 (H+ <50 nmol/L), bicarbonate >15 mmol/L) , Glycosuria, osmotic diuresis with loss of water, sodium, potassium and other electrolytes, Hypovolemia
Management: Management of HHS is similar to that of DKA

Hypoglycemia

Pathogenesis : **Plasma glucose <3.9 mmol/L (<70 mg/dl) ,** Mainly due to Insulin & less frequently sulfonylureas.
Clinical features : sweating , hunger, anxiety, headache, nausea, tiredness, speech difficulty, delirium
Management : (Rule of 15) Give 15 grams of carbohydrates and Wait 15 minutes and re-check glucose . Repeat the same if glucose is still less than 70mg/dL

Retinopathy

Non-proliferative	• Characterized by retinal vascular microaneurysms, blot hemorrhage, and **cotton-wool spots**
Proliferative	• Hypoxemia & neovascularization leading to virtuous hemorrhage, fibrosis, and retinal detachment
Macular edema	• can occur in non proliferative or proliferative stage

Nephropathy

Pathogenesis: Characterized by gradually increasing urinary albumin excretion and blood pressure as the glomerular filtration rate falls insidiously towards end-stage renal disease
Investigation:
- Screen with Urinary Albumin: Creatinine & eGFR Albuminuria (Albumin: Cr >30 mg/g)
- Renal biopsy (Kimmelstiel-Wilson nodules) should be considered in such cases but is rarely necessary or helpful.
- Plasma creatinine level and eGFR should be measured regularly.

Management: ACEI (or ARBs) are recommended to treat nephropathy ,SGLT-2 inhibitors can be used

Neuropathy

Polyneuropathy	• Most common form is **distal symmetric polyneuropathy** • Tingling, numbness, loss of sensation leads to the following: ulcer formation (patients do not shift their weight) with subsequent ischemia of pressure point areas; **Charcot joints.** • Loss of fine touch, proprioception, and vibration. Loss of ankle deep reflex
Mononeuropathies	• Dysfunction of cranial or peripheral nerves • Most often involves **CN III**, but may also involve CN VI and IV. • **Diabetic third nerve palsy:** eye pain, diplopia, ptosis, inability to adduct the eye; but the pupils are spared. • Median nerve neuropathy, ulnar neuropathy, common peroneal neuropathy. • Diabetic lumbosacral plexopathy—severe, deep pain in the thigh; atrophy and weakness in thigh and hip muscles; recovery takes weeks to months. • Diabetic truncal neuropathy—pain in distribution of one of the intercostal nerves.
Autoimmune neuropathy	• **Impotence in men** (most common presentation) • Neurogenic bladder—retention, incontinence • **Gastroparesis**—chronic nausea and vomiting, early satiety. **Give metoclopramide** • Constipation and diarrhea (alternating) • Postural hypotension

Lecture Quiz

Q1: A 29-year-old woman is found unconscious by her partner and rushed to accident and emergency. She is a type 1 diabetic and has maintained excellent glucose control using insulin injections. Blood biochemistry results demonstrate a moderately raised level of insulin, no detectable C-peptide and very low blood glucose. Her partner mentions she is a lawyer and has been working particularly hard in the last week, eating quick meals and occasionally missing meals. The most likely diagnosis is:

A. Hyperosmolar coma
B. Diabetic ketoacidosis
C. Insulin overdose
D. Hypoglycaemic coma

Q2: A 55-year-old diabetic woman presents with altered sensations in her hands and feet. She finds it difficult to turn pages of books and discriminating between different coins. When walking, the floor feels different and she likens the sensation to walking on cotton wool. The most likely diagnosis is:

A. Autonomic neuropathy
B. Diabetic amyotrophy
C. Acute painful neuropathy
D. Symmetrical sensory neuropathy
E. Diabetic mononeuropathy

Q3:A 49-year-old woman presents to her physician's office with a long-standing history of polydipsia, polyuria, central obesity, and hyperlipidemia. She is currently taking metformin, a sulfonylurea, and an angiotensin-converting enzyme (ACE) inhibitor. ACE inhibitors are most beneficial in preventing or slowing the progression of which of the following diabetic complications?

A. Diabetic ketoacidosis
B. Diabetic nephropathy
C. Diabetic neuropathy
D. Diabetic retinopathy
E. Peripheral vascular disease

Q4: What is the most common adverse event of insulin in type 1 diabetes?

A. Hypoglycemia
B. Lipohypertrophy
C.Skin allergy
D.Anxiety or depression

Answers: Q1:D | Q2:D | Q3:B | Q4:A |

Answers Explanation File!

GOOD LUCK !

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