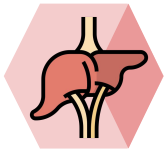
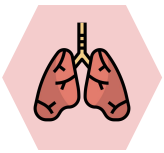
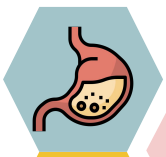
Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Diabetes complications

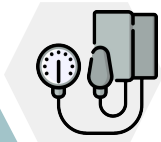




Objectives :

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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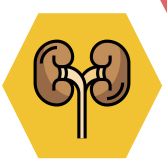
Resources :

Doctors slides: Dr. Mohammed Alsofiani

Books: Step up, Kumar, Master the boards




Introduction

A leading cause of morbidity & mortality, they are divided into acute and chronic:

Diabetes complications	
Acute	**Chronic**
Diabetic ketoacidosis	Microvascular complications
Hyperosmolar hyperglycemic syndrome (HHS or HONK)	Macrovascular complications
Hypoglycemia	

Diabetes is the leading cause for:

- Blindness
- Renal failure
- Non traumatic lower extremity amputation

Somogyi effect vs Dawn phenomenon: Mentioned in Dr Shadins slides only.

Both cause morning <u>hyperglycemia.</u>

The dawn phenomenon:

- Increase in the nocturnal secretion of growth hormone.
- <u>Independent</u> of the Somogyi effect.

The Somogyi

- Rebound response to nocturnal **hypo**glycemia
  - Counterregulatory systems are activated in response to <u>hypo</u>glycemia, leading to morning <u>hyperg</u>lycemia.

If morning hyperglycemia is present

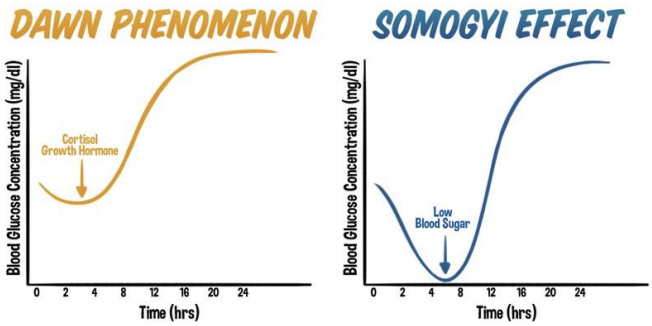
Check the glucose level at 3:00 am:

Glucose level is **elevated:**

- <u>Dawn phenomenon</u>
- Evening insulin should be **increased** to provide additional coverage in the overnight hours.

Glucose level is **low**:

- <u>Somogyi effect</u>
- Evening insulin should be **decreased** to avoid nocturnal hypoglycemia.



Somogyi = **So mu**ch insulin

Dawn = **Down** insulin

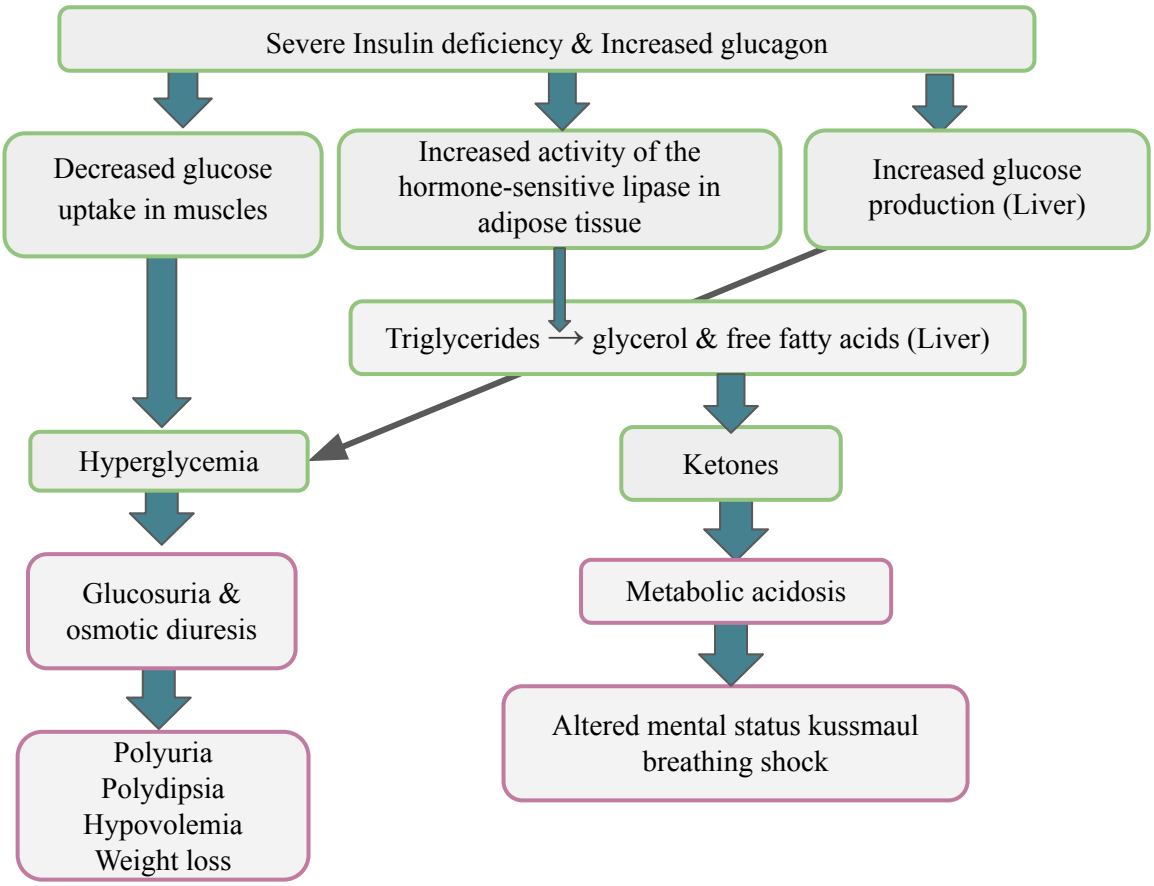
Acute Complications:

Keywords:
Absolute insulin deficiency = No insulin at all = Type 1
Relative insulin deficiency = There is some little insulin = type 2

Diabetic ketoacidosis (DKA):

Status of metabolic acidosis due to **absolute** insulin deficiency in association with **increased levels of glucagon and other counter-regulatory hormones** resulting in increased ketone production Mainly with type 1 rarely with type 2

Pathophysiology:



Insulin deficiency.

- ↑ Hepatic gluconeogenesis.
  - High glucose levels → Osmotic diuresis by the kidneys → Dehydration.
- ↑ Intracellular lipase activity. "Intracellular lipase is inhibited by insulin, when insulin is absent this inhibition is lost"
  - Peripheral lipolysis → ↑ free fatty acids → converted in the liver to acidic ketones → Metabolic acidosis.
- These processes are accelerated by the 'stress hormones' – catecholamines, glucagon and cortisol – which are secreted in response to dehydration and intercurrent illness.

Diabetic ketoacidosis (DKA):

Precipitating factors:

- Previously undiagnosed DM
- Any type of stress or illness
  - **Infectious** process, trauma, myocardial infarction, stroke, recent surgery, sepsis, GI bleeding
- Poor adherence to treatment
- Drugs
  - Corticosteroids, sympathomimetics, atypical anti-psychotics, SGLT-2 inhibitors

Clinical features:

- Polyuria, polydipsia & weight loss
- Nausea and or vomiting
- Abdominal pain
- Change in mental state
- Volume depletion. (Dehydration)
  - Tachycardia, dry mucous membranes, orthostatic hypotension, poor skin turgor
- Hypothermia
- Kussmaul respirations
- Fruity breath

Laboratory findings:

- **Hyperglycemia**
  - Serum glucose >450 mg/dL
- **Metabolic acidosis.**
  - Blood PH <7.3
  - Serum HCO3 <15 mEq/L
- **Ketonemia**
  - Positive serum acetoacetate,
  - B-hydroxybutyrate >3 mmol/L
- **High anion gap**
  - >10
- Urine dipstick
  - Glycosuria, ketonuria
- **Electrolytes**
  - Low total potassium lost as a result of osmotic diuresis
  - But raised serum potassium (do not get fooled!)
  - K+ Shift from intracellular to extracellular compartment with acidosis Insulin therapy moves K+ back into the cells (watch for a drop in K+)

    Because of the absence of the action of insulin, which allows potassium to shift out of cells.
    As insulin is given, it causes a rapid shift of potassium into cells, resulting in a sudden **hypokalemia**.

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

Treatment Of DKA:

- Successful treatment of DKA requires:
  - Correction of dehydration, hyperglycemia, and electrolyte imbalance
  - Identification of comorbid precipitating events
  - Frequent patient monitoring
- Most patients with DKA are treated in ICU
- DKA is associated with increased mortality

- **Rehydration**

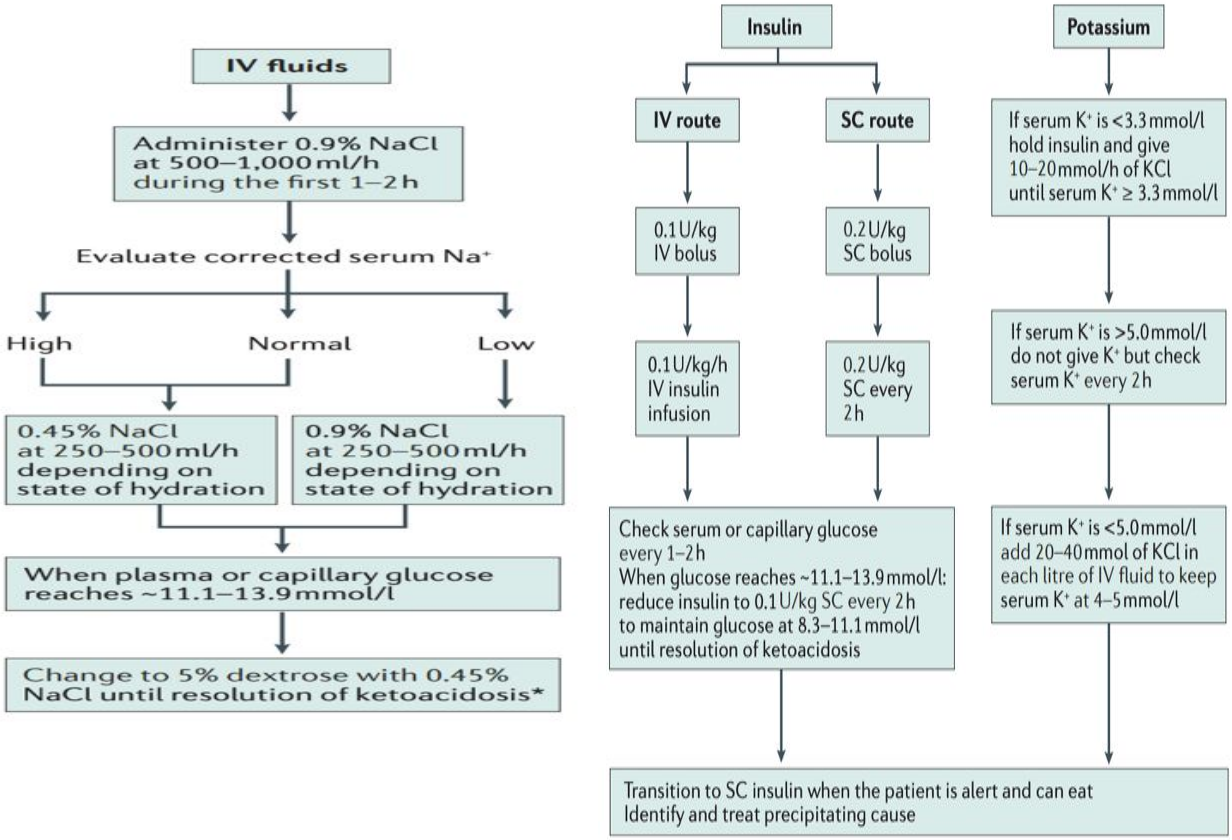
  The first step is rehydrating the patient never give insulin before rehydrating first!!
  Insulin will increase glucose uptake by the cells that will withdraw more water into the cells
  -> More volume depletion.
  - IVF is the most critical step
  - Water deficit is ~ 100 ml/kg of body weight
  - Isotonic saline
    - 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
    - Reduce NaCl to 0.45% and add D5% IVF

- **Electrolytes:**
  - **If K is <3.3 mEq/L, hold insulin and give 20 to 30 mEq/hr until serum K is >3.3**.
  - If **K+ > 5 mmol/L** no need for replacement monitor every 2 hours
  - K+ replacement starts early (when K+ is normal)
  - Rate of K infusion depends on K+ level and eGFR
  - Consider bicarbonate infusion if pH <7
  - Phosphate replacement is almost never required

- **Insulin:**
  - Insulin is the next step after IVF if K is >3.3 **(Never initiate insulin unless K+ is >3.3)**
  - Reduces serum glucose and suppresses ketogenesis
  - Most of the time: we use IV insulin infusion but mild DKA can be treated with subcutaneous insulin
  - Most protocols:
    - IV insulin **bolus 0.1 unit/kg**
    - Followed by: IV insulin **infusion 0.1 unit/kg/h**
  - Continue until **anion gap closes** and metabolic acidosis is corrected

  If the PH and the blood gases become normal, overlap insulin infusion with subcutaneous insulin for 30 minutes. Why? Because if we stop the IV insulin we will have no insulin in the blood in two minutes and the patient will have severe DKA.

Treatment Of DKA: A diagram of the previous slide



Quick recap:

1. Initiate **IV fluids**.
   - Isotonic saline, until plasma glucose is 250 mg/dl then reduce NaCl to 0.45% and add D5%.
2. Potassium:
   - **<3.3 mEq/L**
     - Hold insulin and give 20 to 30 mEq/hr until serum K is >3.3.
   - **3.3 - 5.2 mEq/L**
     - Give potassium with IV fluids to maintain a goal of 4 to 5 mEq/L in serum.
   - **>5.2 mEq/L**
     - Do not give any K with IVF, but continue to monitor every 2 hours.
3. Give **insulin** (hold if K <3.3 as above).
4. Admit to the **ICU** or a very closely monitored floor bed.

- Rapid lowering of glucose can lead to cerebral edema

Hyperosmolar hyperglycemic syndrome HHS: in type 2

Status of **severe hyperglycemia** due to insulin resistance & **relative** insulin deficiency resulting in **increased serum osmolality.**

- 10 times higher mortality than DKA due to patients profile
  - usually older.
  - With comorbidities.
  - Long history of type 2 diabetes, Which may have been unrecognized.
- Develops slower than DKA (over several days)
- **No ketosis**
- Serum glucose level is **higher** than seen in DKA >900 mg/dL
- More severe dehydration & higher plasma osmolality than DKA

Precipitating factors: Same as DKA

- Previously undiagnosed DM
- Any type of stress or illness
  - **Infection**, trauma, myocardial infarction, stroke, recent surgery, sepsis, GI bleeding
- Poor adherence to treatment

Pathophysiology:

- Relative insulin deficiency (there is some detectable insulin in type 2)
  → 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
  → Osmotic diuresis → Severe **dehydration** and plasma **hyperosmolality**
  → impaired consciousness

Clinical features:

- Gradual worsening of polydipsia, polyuria, & weight lost.
- Extreme dehydration and volume depletion
  - Tachycardia, Hypotension, might present with a shock-like state.
- Impaired consciousness is more common than DKA
  - Focal neurologic signs are common
    - Seizures

Laboratory findings:

- **Hyperglycemia:** > 600 mg/dL
- **Hyperosmolarity:** >320 mOsm/L
  The hyperosmolar state predisposes to stroke, MI, or arterial thrombosis, prophylactic subcutaneous **heparin** is given.
- **Serum PH:** >7.3 (No acidosis)
- **No ketones**

Measure	HSS
Plasma glucose level, mmol/l	33.3
Arterial or venous pH	>7.30
Bicarbonate level, mmol/l	>15
Urine or blood acetoacetate (nitroprusside reaction)	Negative or low positive
Urine or blood β-hydroxybutyrate, mmol/l	<3
Effective serum osmolality, mmol/kg*	>320
Anion gap, mmol/l	<12
Alteration in sensorium	Stupor or coma

Management:

Management of HHS is similar to that of DKA

Investigations and treatment are the same as for ketoacidosis, with the exception that a lower rate of insulin infusion (3 units/h) is often sufficient.

Hypoglycemia:

- Plasma glucose <3.9 mmol/L (<70 mg/dl) to convert from mg/dl to mmol/L : 70/18 = 3.9
- **Severe hypoglycemia**
  - need for assistance from another person to correct glucose
- Most frequent & serious adverse effect of 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

Risk factors:

- Longer duration of diabetes
  - Longer duration lead to autonomic neuropathy > unawareness of hypoglycemia
  - **Hypoglycemic unawareness:** in long standing diabetes patient lose the early adrenergic effect and can develop **severe** hypoglycemia without warning
- Older age
  - Usually have renal disease > decrease in creatinine clearance
- Lower levels of glycemia , when achieved with medications insulin
- Erratic timing of meals, including missed meals & low carbohydrate content of meals
- History of recent severe hypoglycemia
- Exercise
- Alcohol ingestion
  - alcohol consuming lead to liver disease therefore there will be no or reduction of glycogen storage.
- Chronic kidney disease (CKD)
- Malnutrition with glycogen depletion
- Insulin & sulfonylureas are the most frequent cause.

Clinical features:

- Sympathetic overactivity
  - Sweating, Tachycardia, Tremors, pallor, palpitations ..etc
- Neuroglycopenic symptoms
  - Irritability, weakness, confusion, convulsion..etc

- The patient could come with chest pain due to IHD because glucose is an important energy source to all the body cells.
- Hypoglycemia could mimic stroke! but once you correct the blood glucose the patient will be recovered

Treatment: (Rule of 15)

- Give **15 grams** of carbohydrates Rapidly absorbed carbohydrates
  - 4 glucose tablets
  - ½ cup of fruit juice or regular soda
  - 1 tablespoon of sugar or honey
- Wait 1**5 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)
- Remember, the patient should not be driving with hypoglycemia or (within 1 hour after treating hypoglycemia)

Unconscious patients require IV dextrose

Chronic Complications:

Vascular complication

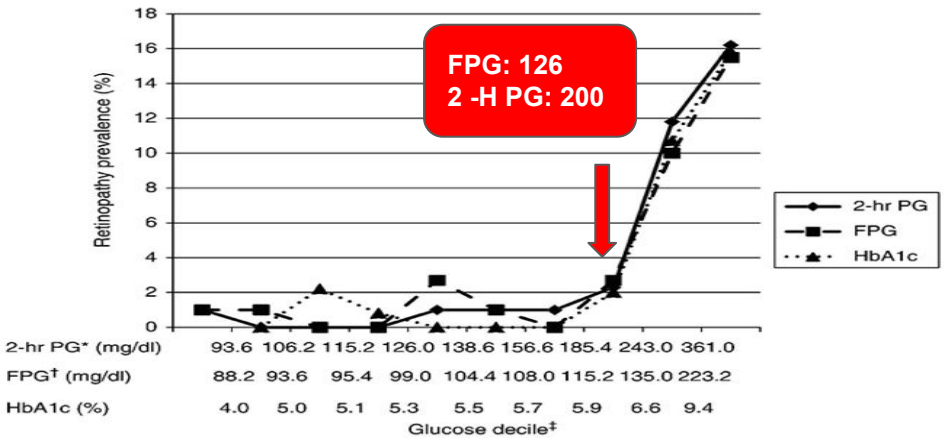
- **Microvascular** (DM **specific**):
  - Retinopathy
  - Nephropathy
  - Neuropathy
- **Macrovascular** (Similar to those in non-DM but occur at greater frequency in DM individuals)
  - Ischemic heart disease Most common cause of death in diabetic patients
  - Peripheral vascular disease
  - Cerebrovascular disease
    - E.g Stroke

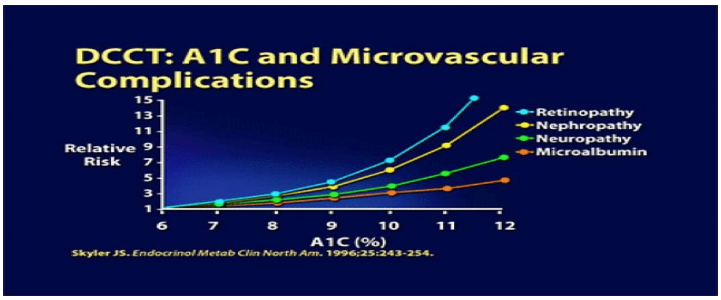
Non-vascular complication

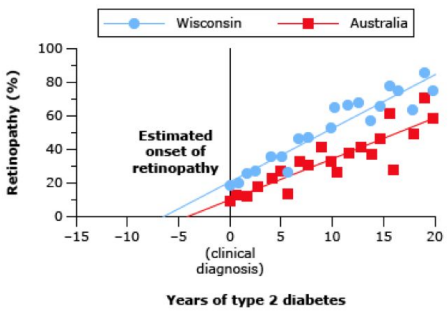
- Gastroparesis
- Recurrent infections
- Hearing loss
- Fatty liver
- Osteoporosis
- Physiological disorders

Insulin resistance lead to macrovascular complications.
Hyperglycemia leads to both macro & micro.
Microvascular complications are more common than Macro

The definition of diabetes is based on risk of retinopathy :







Retinopathy	Non-proliferative: ● Usually appears late in the first decade of the disease or early second decade. ● Characterized by ○ Retinal vascular microaneurysms ○ Blot hemorrhage. ○ Cotton wool spots. Proliferative: ● Hypoxemia → **Neovascularization*** leading to: *Neovascularization is a compensatory mechanism to deliver oxygen and nutrients to the retina ○ vitreous hemorrhage ○ retinal detachment. ○ Fibrosis Macular edema ● can occur in non proliferative or proliferative stage. **Treatment:** ● Prevention (most effective treatment) ● Glycemic and BP control will slow the progression ● Laser Photocoagulation ● Ocular injection ○ (Anti-VEGF therapy for macular edema) to reduce the neovascularization ● Screening: Yearly dilated eye exam.
Nephropathy	● Microalbuminuria: ○ (Albumin: 30 - 300 mg/day) ○ (Albumin-Creatinine ratio .02-.20) ● Macroalbuminuria ● 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 ● Nodular glomerulosclerosis (Kimmelstiel-wilson syndrome) pathognomonic for DM ● **HTN** increase the risk of of progression of diabetic nephropathy to ESRD, BP must be controlled aggressively with ACEi or ARBs **Treatment:** ● Prevention is the most effective therapy. ● Aim is to slow/reverse the disease progression ● Glucose and BP control. ● ACEI or ARBs are recommended to treat nephropathy ● SGLT-2 inhibitors can be used ● Change doses or stop medications that are renally cleared if eGFR is low ● Screen with urinary albumin: creatinine & eGFR

Neuropathy	• Polyneuropathy
	  ○ Most common form is **distal symmetric polyneuropathy.**
	  ○ Tingling, numbness, loss of sensation.
	  ○ Loss of fine touch proprioception, vibration, and deep ankle reflex.
	  ○ up to 50% have no symptoms.
	• Mononeuropathy
	  ○ Dysfunction of cranial or peripheral nerve.
	  ■ e.g. 3rd cranial nerve palsy.
	  ● Eye pain, diplopia, ptosis, inability to adduct the eye, but **pupils are spared**
	  ○ less common than the polyneuropathy
	• Autonomic neuropathy
	  ○ Impotence in men (most common presentation)
	  ○ Neurogenic bladder
	  ■ retention, incontinence
	  ○ Gastroparesis
	  ■ chronic nausea and vomiting, early satiety
	  ○ Constipation and diarrhea (alternating)
	  ○ Postural hypotension

How to prevent these complications:

UKPDS: <u>Type 2</u> 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%?)

Results:

- **Intensive glucose therapy (lowering A1C to 7%):**
  - Less Microvascular complications by 25% (after 15 years)
  - Less Microalbuminuria by 33% after 12 years
  - Any diabetes-related endpoint are less by 12%
  - There was a direct relationship between the glucose level and risk of vascular complications
  - 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:**
  - Less Death by 32%
  - Less Stroke by 44%
  - Less microvascular complications by 37%
  - Less Heart Failure by 56%
  - Less Retinopathy progression by 34%
  - Any diabetes-related endpoint are less by 24%

How to prevent these complications cont:

DCCT: Type 1 diabetes & complications:

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

When & how to screen for the diabetes complications:

Type 2

- Start screening for complications **at time** of diagnosis:
  - Yearly Dilated Eye Exam
  - Yearly Albumin:Cr ratio & Serum Creatinine
  - Yearly foot exam (ask the patient to examine feet, routinely)
  - Other screening tests if clinically indicated

Type 1

The same but start screening **5 years after** the time of diagnosis

How to reduce the risk of diabetes complications: Important

- Early Diagnosis & Routine Screening Tests
- Maintain a good glucose control
  - **(A1C around 7%)**
- Maintain a good BP control
  - **(ACE or ARB) (< 130/80)***
- Maintain a good control of lipid
  - **(statin)**
- Smoking cessation
- **Aspirin**
  - (only in patient with high CVD risk)
- Physical activity

* In doctors slides its 140/90.

* Doctors Explanation:
  - Optimal BP is debatable, so in clinical practice
  - **<130/80** in Patients with:
    - Prior history of CVD, Multiple risk factors of CVD (e.g. HTN, Dyslipidemia, smoking), Albuminuria, Family history of premature CVD.
  - **<140/90** in patients who don't have any of the above.

Summary

Diabetes Mellitus Complications

Acute	Chronic
Diabetic Ketoacidosis	Microvascular: • Retinopathy • Nephropathy • Neuropathy
Hyperosmolar hyperglycemic syndrome	Macrovascular: • Coronary heart disease • Peripheral vascular disease • Cerebrovascular disease
Hypoglycemia	Non-vascular: • Gastroparesis • Infections • Skin Changes • Hearing loss • Others

Comparison between Nonketotic Hyperosmolar Syndrome (NKHS) and Diabetic Ketoacidosis (DKA)

	NKHS	DKA
Glucose level	Extremely elevated	Extremely elevated
Best initial therapy	Insulin + High-volume fluids	Insulin + High-volume fluids
Hypertonicity alters mental status	Yes	Yes
Hypertonicity causes seizures and brain abnormalities	More common	Less common
Anion gap	Normal	Elevated
Serum bicarbonate	Normal	Low

Questions

Q1) What is the most common adverse event of insulin in type 1 diabetes?
A-Hypoglycemia
B-Lipohypertrophy
C-Skin allergy
D-Anxiety or depression

Q2) A 63 years old diabetic male presented to his local doctor due to intermittent leg pain, which was relieved by resting. Negative dorsalis pedis. Which of the following could be the the cause of this complication?
A-Autoimmune vasculitis
B-Deep vein thrombosis
C-Atherosclerosis
D-Neuropathy

Q3) A 57-year-old man is admitted to the intensive care unit with altered mental status, hyperventilation, and a markedly elevated glucose level.
Which of the following is the most accurate measure of the severity of his condition?
A-Glucose level.
B-Serum bicarbonate.
C-Urine ketones.
D-Blood ketones.

Q4) A 59-year old female who has diabetes mellitus for more than 25 years. Recently she began to complain of decreasing visual acuity. She has no eye pain and her intraocular pressure is normal. Which of the following lesion could be the possible cause?
A-Cytomegalovirus retinitis
B-Proliferative retinopathy
C-Glaucoma
D-Conjunctivitis

Q5) What is primary cause of diabetic complication including retinopathy , nephropathy and peripheral neuropathy?
A-Low immunity
B-Microangiopathy
C-Atheroma
D-Systemic disturbances

Q6) Which of the following measures does not help to prevent diabetes complications?
A-Controlling blood glucose
B-Controlling blood pressure and blood lipids
C-Eliminating all carbohydrates from the diet
D-Prompt detection of diabetic eye and kidney disease

Q7) Which of the following is a common and recognized renal complication of diabetes mellitus?
A-Nodular glomerulosclerosis
B-Nodular glomerulonephritis
C-Armani-Epstein
D-Renal papillary necrosis

Q8) Which of the following are the recommended blood pressure and lipid goals for the prevention of cardiovascular disease in adults with diabetes?
A-BP < 140/90, Trig <150, LDL < 100
B-BP < 130/85, Trig < 300, LDL < 100
C-BP < 135/80, Trig < 200, LDL < 130
D-BP < 130/80, Trig <150, LDL < 100

Q9)What medical conditions can cause Hyperglycemic Hyperosmolar non-ketotic?
A-Acute hypoglycemia
B-DM type 1
C-Third degree burns
D-Acute Pancreatitis and Severe burns

Q10) Patient presented with low PH, low Pco2 and ketones in urine. What is the best initial management?
A-IV fluids
B-IV fluids with insulin
C-Metformin
D-Premixed insulin

Answers: 1-A 2-C 3-B 4-B 5-B 6-B 7-A 8-D 9-D 10-A