

Diabetes complications

AHLAM HAMDI DAHADHA

Acute complications of DM

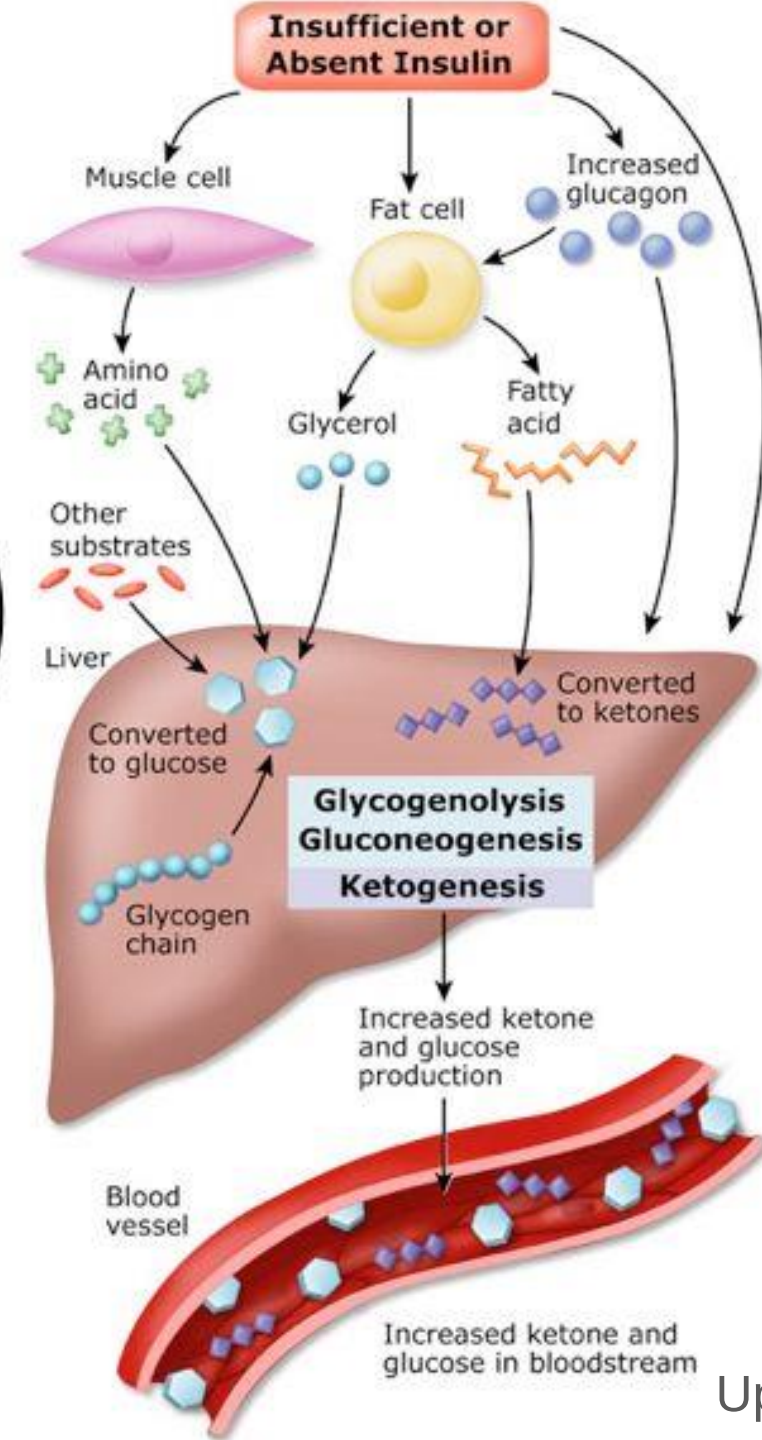
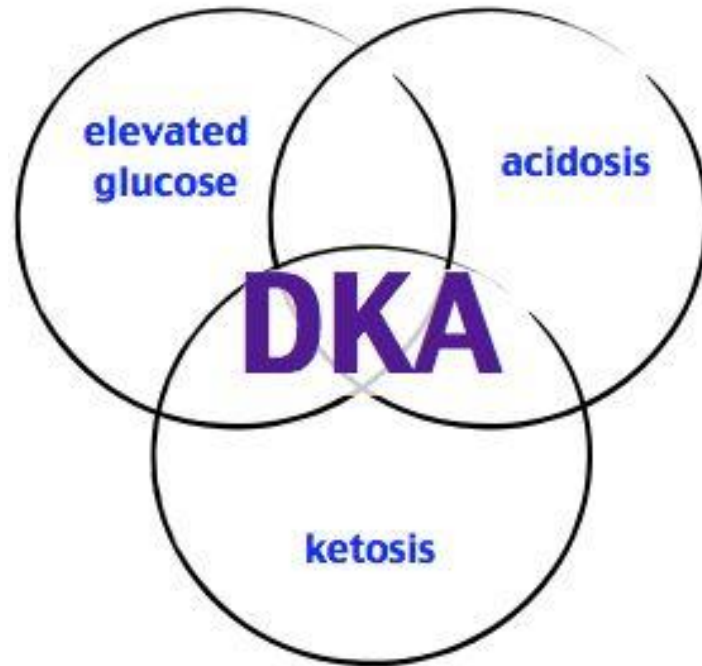
Diabetic ketoacidosis (DKA)

- A state of **severely uncontrolled** diabetes caused by insulin deficiency.
- Characterised by **hyperglycaemia**, **hyperketonaemia** and **metabolic acidosis**
- It has been divided into mild, moderate and severe based upon biochemical and clinical features.

Diabetic ketoacidosis (DKA)

- Serum glucose concentration is usually **> 500 mg/dL and <800 mg/dL**.
- However, glucose concentrations **may exceed 900 mg/dL** in patients who are comatose.
- Glucose may be **mildly elevated** in special cases of DKA such as; starvation or pregnancy.

Diabetic Ketoacidosis



Diabetic ketoacidosis (DKA)

- DKA is mainly associated with DM I.
- Also occurs in DM II under conditions of extreme stress such as serious infection, trauma, CVD or other emergencies.
- **Less often as a presenting manifestation in a disorder called “ketosis-prone diabetes mellitus”.**

Diabetic ketoacidosis (DKA)

Ketosis prone diabetes (KPD)

→ comprises a group of atypical diabetes syndromes characterized by **severe beta cell dysfunction** (manifested by presentation with DKA) and a variable clinical course.

→ These syndromes do not fit the traditional categories of diabetes defined by the ADA.

Diabetic ketoacidosis (DKA)

Ketosis prone diabetes (KPD)

→ It can account for 25 – 50% of African American or Hispanic cases of DKA.

Box 12.1 Features of ketosis-prone type 2 diabetes mellitus

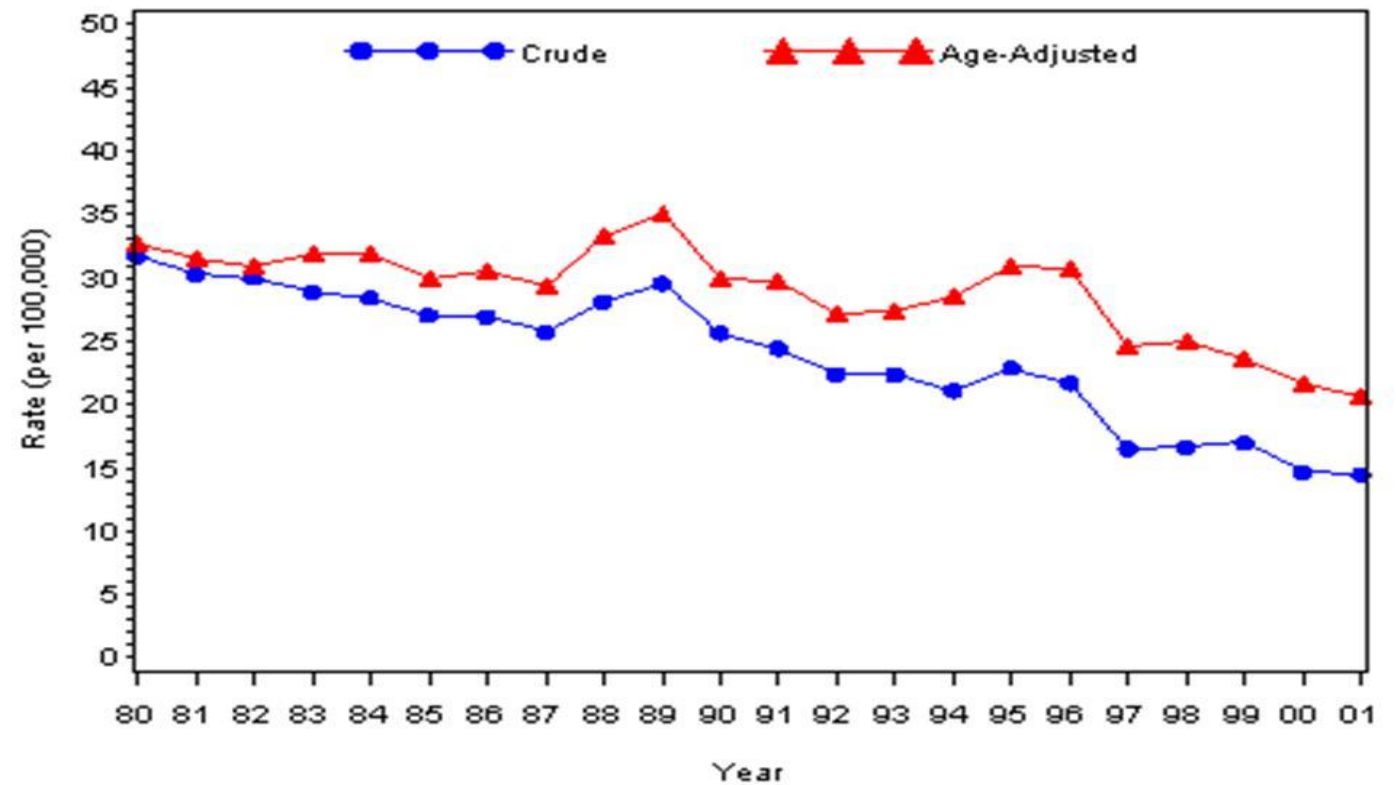
- Acute presentation
- Mean age >40 years
- Male preponderance
- BMI ≥ 28 (for African American, less for Hispanic and Taiwanese)
- Mostly newly diagnosed with diabetes
- Strong family history of type 2 diabetes
- HbA_{1c} at presentation >12%
- Autoimmune markers for type 1 diabetes negative
- Fasting C-peptide detectable
- Most do not require long-term insulin therapy

Diabetic ketoacidosis (DKA)

- More common in young (<65 years) diabetic patients.
- More common in women compared to men.
- Incidence rates of 1 – 5% have been reported worldwide, and frequency is increasing.
- **DKA accounts for more than 50% of all deaths in people with type 1 diabetes < 24 years of age in the USA.**

Diabetic ketoacidosis (DKA)

DKA mortality per 100,000 diabetic patients declined between 1985 and 2005 with the greatest reduction in mortality >65 years



Diabetic ketoacidosis (DKA)/Precipitating factors

Inadequate insulin treatment or noncompliance
New onset diabetes (20 to 25%)
Acute illness
Infection (30 to 40 percent)
Cerebral vascular accident
Myocardial infarction
Acute pancreatitis
Drugs
Clozapine or olanzapine
Cocaine
Lithium
Terbutaline

Diabetic ketoacidosis (DKA)

- The most common events are infection (often pneumonia or urinary tract infection) and discontinuation of or inadequate insulin therapy.
- Two hormonal abnormalities are involved:
 - Insulin deficiency and/or resistance.
 - Glucagon excess, which may result from removal of the normal suppressive effect of insulin.
- In addition, increased secretion of catecholamines and cortisol can contribute to the increases in glucose and ketoacid production.

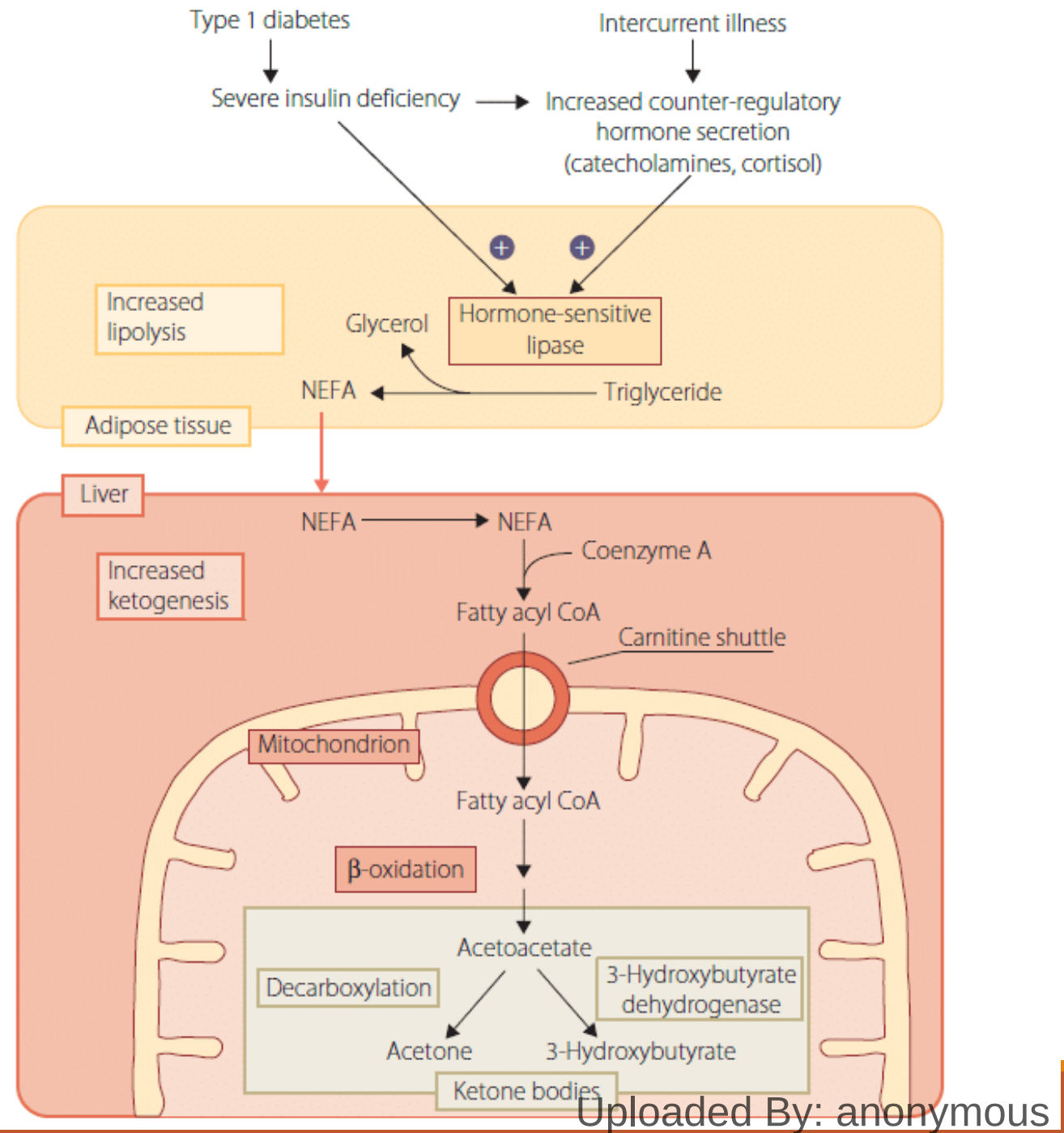
Diabetic ketoacidosis (DKA)

- Glucagon and catecholamines, (also growth hormone and cortisol) leads to hepatic overproduction of glucose and ketones.
- Lack of insulin combined with excess stress hormones promotes lipolysis, with the release of NEFAs from adipose tissue into the circulation.
- In the liver, fatty acids are partially oxidised to the ketone bodies which contribute to the acidosis, and acetone

Diabetic ketoacidosis (DKA)

- **Hyperglycaemia** results from increased glycogenolysis secondary to glucagon excess
 - gluconeogenesis as a result of
 - Increased lipolysis and proteolysis
 - Diminished peripheral uptake of glucose due to absent insulin stimulated uptake
 - and utilization of alternative fuels such as NEFA and ketone bodies in preference to glucose.

Diabetic ketoacidosis (DKA)/Mechanism



Diabetic ketoacidosis (DKA)

- Hyperglycaemia causes an **osmotic diuresis** that leads to dehydration and loss of electrolytes.
- Na depletion is worsened because of diminished renal Na reabsorption due to insulin deficiency.
- **Metabolic acidosis** leads to the loss of intracellular K^+ in exchange for H^+ and increased K^+ in the blood

Diabetic ketoacidosis (DKA)/ clinical features

- DKA usually evolves rapidly, over a 24-hour period.
- The earliest symptoms are **polyuria, polydipsia, and weight loss.**
- As hyperglycemia progresses, **neurologic symptoms**, including lethargy, confusion & drowsiness which can progress to coma.
- **Hyperventilation and abdominal pain.**

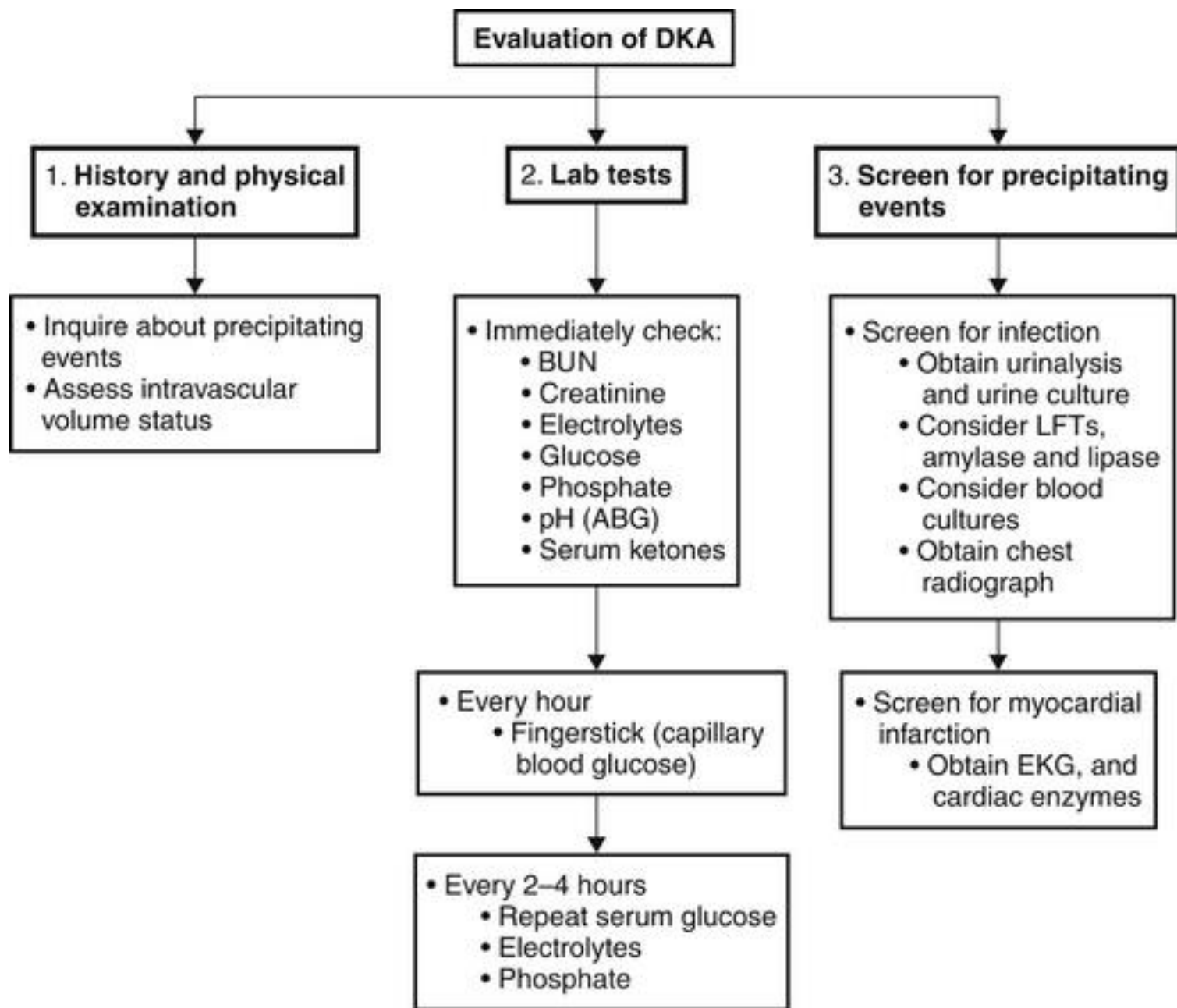
Box 12.2 Clinical features of diabetic ketacidosis

- Polyuria and nocturia; thirst
- Weight loss
- Weakness
- Blurred vision
- Acidotic (Kussmaul) respiration
- Abdominal pain, especially in children
- Leg cramps
- Nausea and vomiting
- Confusion and drowsiness
- Coma (10% of cases)

Diabetic ketoacidosis (DKA) / Evaluation

Initial evaluation — DKA is a medical emergency that require prompt recognition and management. An initial history and rapid but careful physical examination should focus on:

- Airway, breathing, and circulation (ABC) status
- Mental status
- Possible precipitating events (eg, source of infection, myocardial infarction)
- Volume status



Diabetic ketoacidosis (DKA)/ Abdominal pain

- Patients with DKA may present with nausea, vomiting, and abdominal pain; more common in children.
- Associated with the severity of the metabolic acidosis.
- Possible causes include delayed gastric emptying induced by the metabolic acidosis and associated electrolyte abnormalities.

Diabetic ketoacidosis (DKA)/Physical exam

- Signs of volume depletion → decreased skin turgor, dry axillae and oral mucosa, low jugular venous pressure and, if severe, hypotension.
 - Patients may have a fruity odor (due to exhaled acetone and similar to nail polish remover).
 - Deep respirations reflecting the compensatory hyperventilation.
- Fever is rare even in the presence of infection, because of peripheral vasoconstriction due to hypovolemia.

Diabetic ketoacidosis (DKA)/ Lab results

- **Hyperglycemia and hyperosmolality** are the two primary laboratory findings.
- The impact of hyperglycemia, insulin deficiency, osmotic diuresis, and fluid intake leads to variability in laboratory findings

DKA - Laboratory findings

Blood Glucose	>13.8 mmol/L (250mg/dL)
Ketones	Urine: moderate to large Blood: >3mmol/L
Osmolality	Increased – high blood glucose and urea/creatinine, dehydration
Electrolytes	Low/normal Na ⁺ and Cl ⁻ Low/normal/high K ⁺ (often misleading) Low HCO ₃ (normal 23-31)
Anion Gap	≥10 mild >12 moderate to severe
Blood Gases	pH ≤7.3, HCO ₃ ≤15 (mild) pH <7.0, HCO ₃ <10 (severe)

(Kitabchi, Guillermo, Umpierrez, Fisher, 2009)

Interpretation of Laboratory findings

Results	Interpretation
Hyperglycemia	Confirm the diagnosis of DKA
Glucosuria	
Ketonemia	
Ketonuria	
↓ pH	Severe metabolic acidosis due to ↑ production of ketone bodies
↓ bicarbonate and PCO ₂	Metabolic acidosis with partial respiratory compensation (the hyperventilation)
↑ anion gap	Due to ↑ ketone bodies in the blood
↑ urea & creatinine	1. Renal impairment (dehydration → ↓ blood volume → ↓ renal perfusion) 2. Dehydration 3. Degradation of protein (for urea)
↑ K ⁺	↓ Uptake of potassium by cells in the absence of insulin
↑ Plasma osmolality	Due to hyperglycemia and fluid loss

Diabetic ketoacidosis (DKA)/ Treatment

- Initial treatment involves rehydration, usually with isotonic saline (0.9%) with appropriate supplements.
- Initial serum potassium levels may be normal or even high
 - There will be an overall deficiency, and replacement should commence more or less immediately
 - Serum potassium will fall with treatment as a result of correction of acidosis and insulin administration, both of which increase cellular uptake.
 - Careful and regular monitoring of serum potassium is essential as treatment - induced hypokalaemia is a significant cause of cardiac dysrhythmia and even death

Diabetic ketoacidosis (DKA)/ Treatment

- Regular/soluble insulin is usually given by continuous infusion
- Search for and treat precipitating cause (e.g. infection, myocardial infarction)
- Hypotension usually responds to adequate fluid replacement.
- Central venous pressure monitoring in elderly patients or if cardiac disease present
- NG tube if conscious level impaired, to avoid aspiration of gastric contents

Diabetic ketoacidosis (DKA)/ Treatment

- Urinary catheter if conscious level impaired or no urine passed within 4h of start of therapy
- Continuous ECG monitoring may warn of hyper - or hypokalaemia
- Adult respiratory distress syndrome – mechanical ventilation (100% O₂, IPPV), avoid fluid overload
- Mannitol (up to 1 g/kg IV) if cerebral oedema suspected.
- Treat specific thromboembolic complications if they occur

Hyperosmolar hyperglycemic syndrome (HHS)

- **Severe hyperglycemia and dehydration with the absence of ketosis or mild ketosis.**
- Patients are unable to recognize thirst to replace fluids due to age, illness, sedation or incapacity.
- Dehydration exacerbates hyperglycemia might reach 600mg/dl and may reach 1000mg/dl sometimes
- Blood becomes so osmolar that might cause impaired reflexes, motor impairments, verbal inability and seizures.

Hyperosmolar hyperglycemic syndrome

- Sometimes it is the first sign of DM.
- Similar to DKA (precipitated by infection, illness)
- Similar treatments, but might take more time to resolve (a week or longer).
 - Patients may present with significant hypernatraemia (serum sodium > 150 mmol/L) in which case either (hypotonic saline) or 5% (isotonic) dextrose is given.
 - Only 1 – 2 liters of hypotonic saline should be used as otherwise a too rapid reduction in osmolality may cause pulmonary or cerebral edema
- The absence of clinical symptoms may delay diagnosis.

Hyperosmolar hyperglycemic syndrome

- Around 25% of patients with HHS have newly diagnosed diabetes.
→ is unusual, accounting for < 1% of hospital admissions.
- Mortality is high (5 – 20%), partly because of age and underlying cause often cardiovascular disease or serious infection.

Hypoglycemia

- Low blood glucose
 - Most commonly in type 1 diabetes, but can occur in both
 - Improper management rather than the disease itself.
 - Over dosage of insulin or antidiabetic drug
 - Main cause of Coma and results in 3-4% of deaths specially at night.

Hypoglycemia

- A major factor preventing patients with type 1 and 2 diabetes from achieving near normoglycaemia.
- Hypoglycaemia is more common in young children
 - May be responsible for the cognitive impairment and lowered academic achievement in children diagnosed with diabetes under the age of 5 years

Hypoglycemia

- **Nocturnal hypoglycemia** — Most episodes of severe hypoglycemia occur during sleep
- Frequent even with the use of continuous subcutaneous insulin infusion or a basal-bolus regimen with insulin analogues

Hypoglycemia/ symptoms



Hypoglycemia/ Consequences

Box 13.1 Some consequences of hypoglycaemia in diabetes

- Obstacle to achieving normoglycaemia
- Disabling symptoms
- Sudden death syndrome
- Cognitive impairment in children
- Major source of anxiety in patients

Hypoglycemia/ Consequences

Neurological Consequences of Hypoglycemia

Short-term:

- Cognitive dysfunction
- Behavioural abnormalities
- Confusional state
- Coma
- Seizures
- TIAs; transient hemiplegia
- Focal neurological deficits (rare)

Long-term:

- Cerebrovascular events – hemiparesis
- Focal neurological deficits
- Ataxia; choreoathetosis
- Epilepsy (rare)
- Vegetative state (rare)
- Cognitive impairment with behavioural and psychosocial problems

TIA, transient ischaemic attack

Frier. *Diabetes and the Brain*; Eds Biessels & Luchsinger 2010:131–57

Hypoglycemia/ Treatment

- **Blood glucose <70 mg/dL**
- Pt should use 10 to 15 g of fast-acting CHO for glucose levels of 51 to 70 mg/dL,
- 20 to 30 g of CHO for blood glucose levels ≤ 50 mg/dL.
- Retest 15 minutes after and repeat treatment as needed based on blood sugar levels.
- Once blood glucose is >70 mg/dL, the patient should use the appropriate insulin dose to cover CHO intake at the meal.

Hypoglycemia/ Treatment

If the meal following the hypoglycemic episode delayed:

→ A snack containing another 15 grams of carbohydrate should be consumed.

→ A pattern of overtreating hypoglycemia can result in a greater than desired rise in blood glucose and increased calorie intake, resulting in weight gain.

Chronic complications of DM

Chronic complications – Introduction

→ Chronic diabetes result in the development of tissue complications mainly microvascular disease and macrovascular disease.

- Microvascular diseases include:
 - Microangiopathy
 - Retinopathy
 - Nephropathy
 - Neuropathy
- Macrovascular disease such as Atherosclerosis

Chronic complications – Introduction

- Microangiopathy
 - Progressive occlusion of the vascular lumen
 - Increased vascular permeability
 - basement membrane thickening
- Microvascular disease is related to the **duration** and **severity** of hyperglycemia
- Hypertensive patients are more prone to the development of complications

Chronic complications – Introduction

- **Advanced glycation end products (AGEs)** are formed by the reaction of glucose and other glycating compounds, such as methylglyoxal, with proteins and other long – lived molecules, such as nucleic acids.
- Early glycation products are reversible, but eventually they undergo irreversible change through cross - linking

Chronic complications – Introduction

- AGEs alter cellular protein function by cross linking extracellular matrix especially collagen and laminin
 - Increase thickness and permeability, reduce elasticity
- They bind to specific receptors on several types of cells (macrophages, endothelial cells and glomerular cells)
- Generation of reactive oxygen species, activation of Protein Kinase C and other inflammatory markers.

Chronic complications – Introduction

- Reactive oxygen species activate transcription factor NF Kappa B (inflammatory pathway).
- In macrophages it stimulates Cytokines production and thus Inflammation.
- In artery walls NF kappa B stimulate inflammatory cell adhesion and increase vascular permeability.

The 4 hypotheses of diabetic complications*

1. Increased activity of aldose reductase
• (sorbitol pathway)

1. Formation of reactive oxygen species
• ('free-radicals')

1. Activation of protein kinase C
• (PKC)

1. Increased production of advanced glycation end-products (AGE)

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Microvascular Complications

Retinopathy

- A highly specific vascular complication of both DM I & II .
- Prevalence strongly related to duration of diabetes.
- The most frequent cause of new cases of blindness among adults aged 20–74 years
- Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in DM.
- In addition to duration of diabetes, other risk factors include chronic hyperglycemia, the presence of nephropathy, and hypertension

Retinopathy

To reduce the risk or slow the progression of retinopathy:

- Optimize glycemic control
- Optimize blood pressure control

Retinopathy

Screening:

Initial dilated and comprehensive eye examination by an ophthalmologist or optometrist:

- Adults with type 1 diabetes, within 5 years of diabetes onset.
- Patients with type 2 diabetes at the time of diabetes diagnosis.

Retinopathy

Screening (2):

- If no evidence of retinopathy for one or more eye exam, exams **every 2 years may be considered**.
- If diabetic retinopathy is present, **subsequent examinations should be repeated at least annually** by an ophthalmologist or optometrist.
- More frequent exams → If retinopathy is progressing or sight-threatening.

Retinopathy

- Retinal photography may serve as a screening tool for retinopathy, but is not a substitute for a comprehensive eye exam.



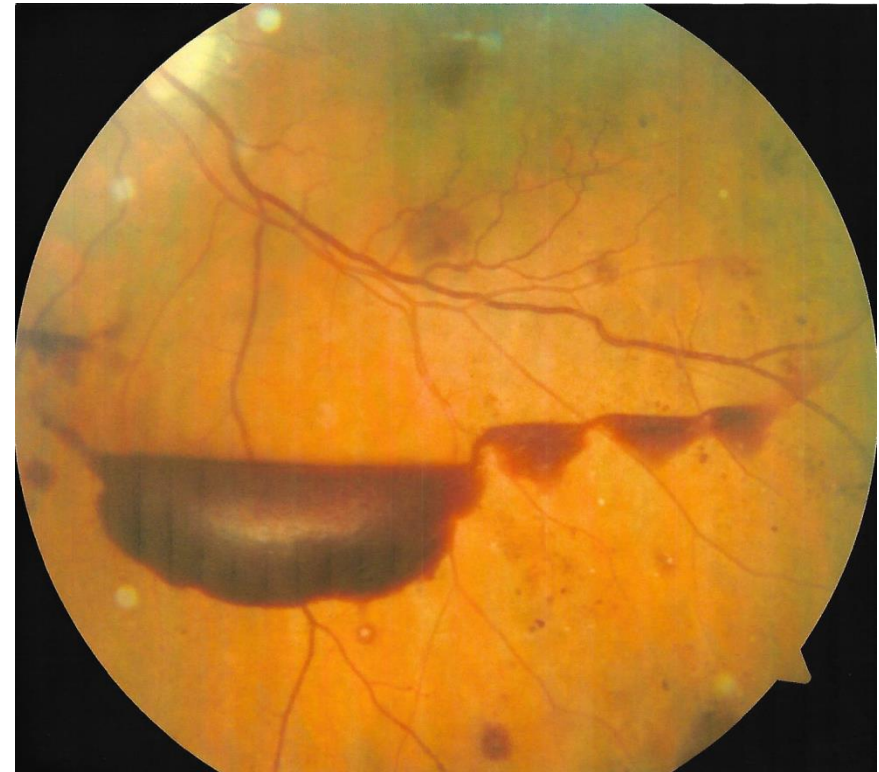
Retinopathy

Divided into two major forms:

- ✓ Nonproliferative retinopathy (NPDR)- cotton wool spots, intraretinal hemorrhages
- ✓ Proliferative diabetic retinopathy (PDR) - hemorrhage & fibrosis

→ Named for the absence or presence of **abnormal new blood vessels emanating from the retina**.

Retinopathy



Retinopathy- treatment

- Refer patients with severe NPDR, or any PDR to an ophthalmologist experienced in management of diabetic retinopathy.
- **Laser photocoagulation therapy** is indicated to reduce the risk of vision loss.
- Special care in pregnancy → fast progression.