Acute Complications of DM

Hashem Hanaqtah Samer Balasmeh Rahaf Masandah

- **Covered Topics:**

1) Diabetic ketoacidosis (DKA)

2) Hyperosmolar Hyperglycemic Non-ketotic Syndrome (HHNS)

3) Hypoglycemia

Diabetic Ketoacidosis (DKA)

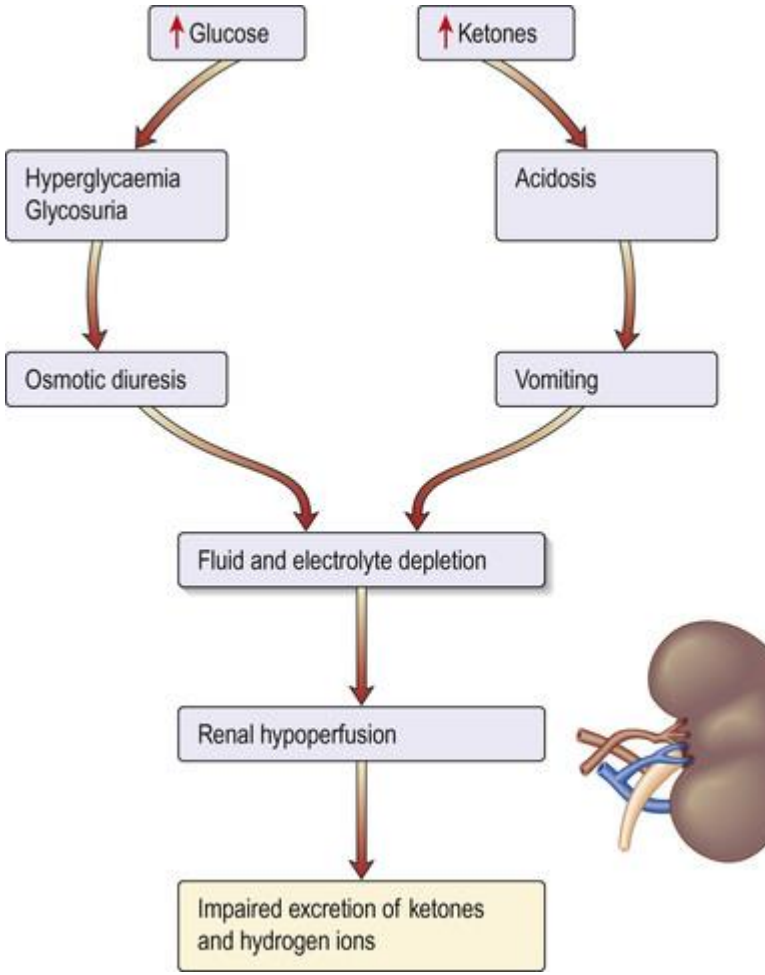
Diabetic Ketoacidosis

- DKA is an acute life-threatening medical emergency that can occur in both DM type 1 and type 2, but **mostly in type 1**.

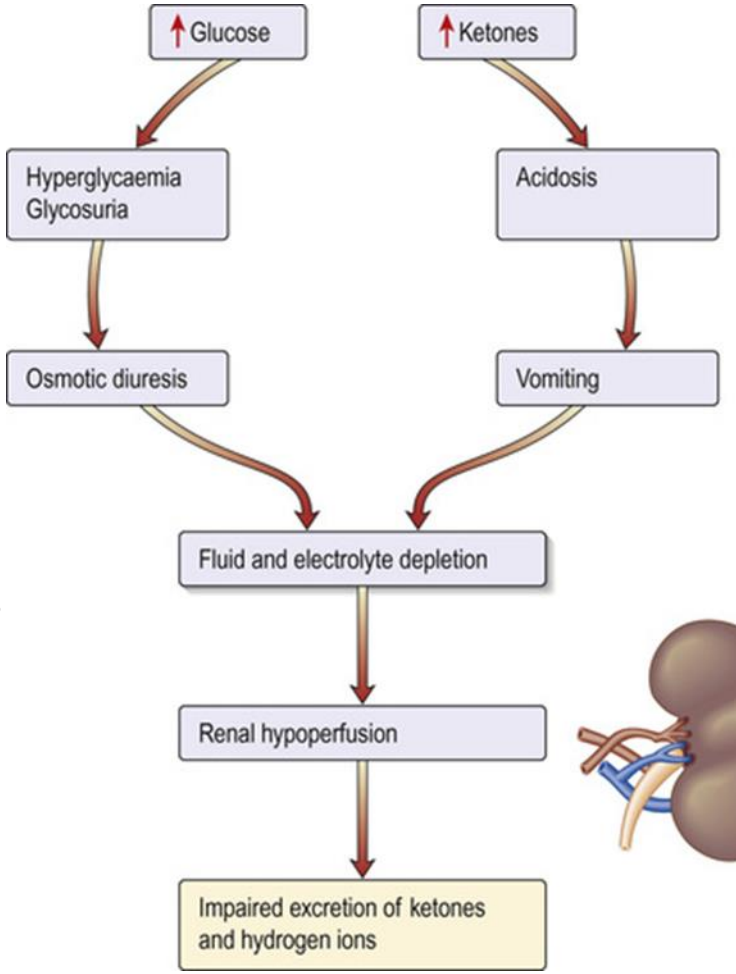
- **Etiology**
- Lack of or insufficient insulin replacement therapy
  - Undiagnosed, untreated diabetes mellitus
  - Treatment failure / Poor adherence in known diabetics
- Increased insulin demand
  - Stress: infections, surgery, trauma, myocardial infarction , burns, heatstroke
  - Drugs: glucocorticoid therapy, cocaine use, alcohol abuse

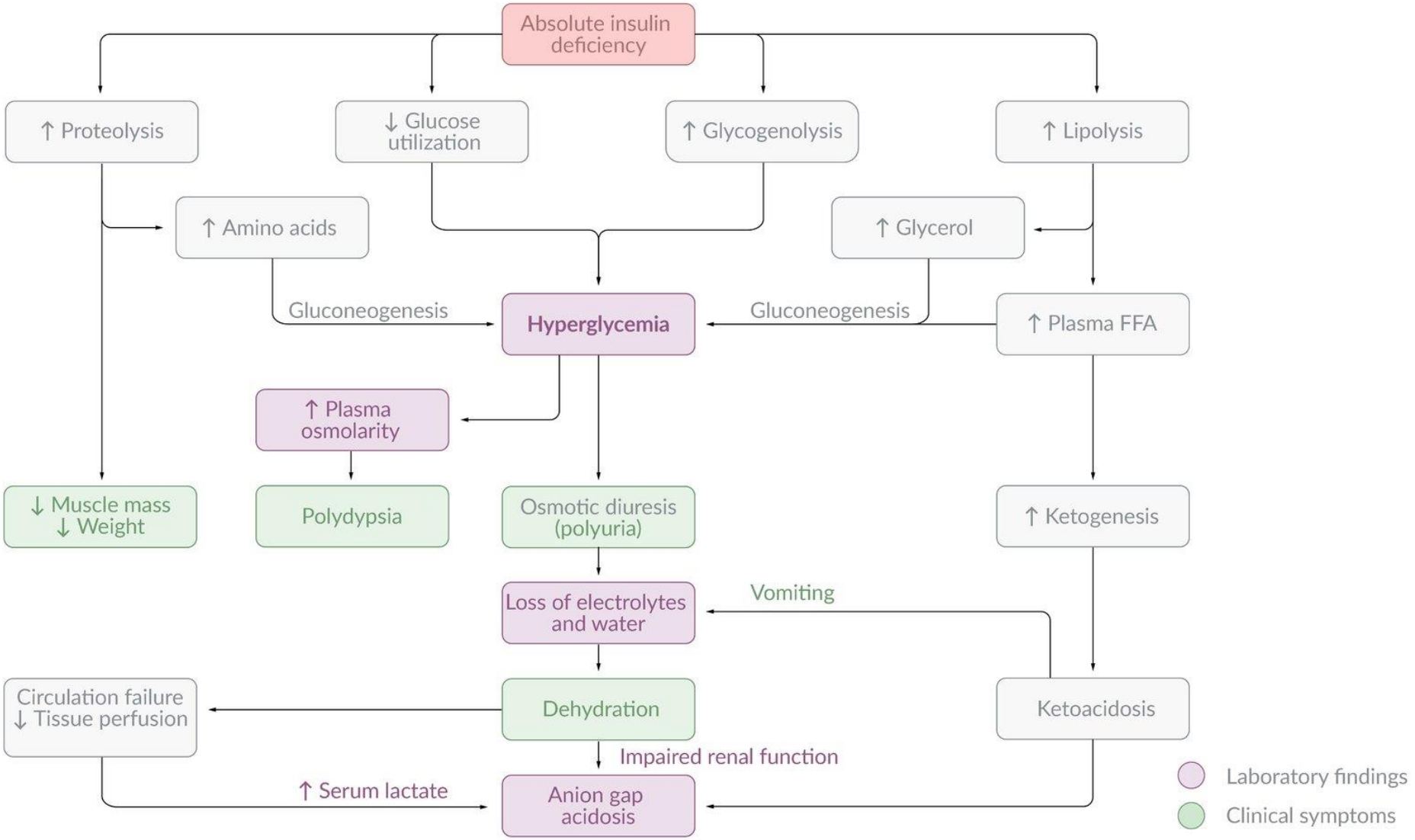
Pathogenesis

- Insulin normally elevates cellular uptake of glucose from the blood.
- In the insulin-deficient state of DKA, hyperglycemia occurs
- Hyperglycemia, in turn, leads to progressive volume depletion via osmotic diuresis



- Insulin deficiency also increases fat breakdown (lipolysis).
- the free fatty acids generated by lipolysis become ketones (acetoacetate & B-hydroxybutyrate)
- Serum bicarbonate is consumed for the acidic ketones.Metabolic acidosis with an elevated anion gap is characteristic of DKA




Absolute insulin deficiency
↑ Proteolysis
↓ Glucose utilization
↑ Glycogenolysis
↑ Lipolysis
↑ Amino acids
↑ Glycerol
Gluconeogenesis
Hyperglycemia
Gluconeogenesis
↑ Plasma FFA
↑ Plasma osmolarity
↓ Muscle mass
↓ Weight
Polydypsia
Osmotic diuresis (polyuria)
↑ Ketogenesis
Loss of electrolytes and water
Vomiting
Circulation failure
↓ Tissue perfusion
Dehydration
Ketoacidosis
Impaired renal function
↑ Serum lactate
Anion gap acidosis
Laboratory findings
Clinical symptoms

Clinical Features

20.14 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
- Delirium, drowsiness, coma (10%)

Clinical Features

- Specific findings in DKA over HHS
  - Rapid onset (< 24 h) in contrast to HHS
  - Abdominal pain
  - Fruity odor on the breath (from exhaled acetone)
  - Hyperventilation: long, deep breaths (Kussmaul respirations)

Diagnostic Approach

- Check serum glucose to confirm hyperglycemia.
- Check BMP for serum bicarbonate, anion gap, electrolytes, and renal function.
- Check for the presence of ketones.
  - Urine ketones: Standard urine dipstick assays detect acetoacetate and acetone but not beta-hydroxybutyrate.
  - Serum beta-hydroxybutyrate
- Check blood gas analysis for pH.
- Diagnostic workup to evaluate the underlying cause: HbA1c, CBC, ECG, infectious workup

Diagnostic criteria

Diagnostic criteria for DKA and HHS			
Laboratory test		**DKA**	**HHS**
BMP	**Glucose**	• **< 600 mg/dL** (< 33.3 mmol/L) • About 10% of patients with DKA will be euglycemic (e.g., glucose ≤ 250 mg/dL) [2]	• **> 600 mg/dL** (> 33.3 mmol/L)
	Bicarbonate	• < 18 mEq/L (< 18 mmol/L)	• > 18 mEq/L (> 18 mmol/L)
	Anion gap	• **Elevated anion gap** > 10 mEq/L (> 10 mmol/L)	• Normal anion gap < 10 mEq/L (< 10 mmol/L)
Urinalysis		• Moderate-large **urine ketones** (ketonuria) • Glucosuria	• Negative or small ketones • Glucosuria
Serum β-hydroxybutyrate		• Elevated	• Normal
Blood gas		• pH ≤ 7.30	• pH > 7.30
Serum osmolality		• Normal or mildly elevated	• **Elevated** > 320 mosm/kg (> 320 mmol/kg)

Electrolytes and renal function

- Sodium
  - Hyponatremia is common in both DKA and HHS , due to hypovolemic hyponatremia ; and hypertonic hyponatremia
  - Always check corrected sodium for hyperglycemia
- Potassium in DKA: normal or elevated (despite a total body deficit)
- Magnesium levels are typically low.
- Phosphorus levels may be elevated despite a total body deficit.
- BUN and creatinine are often elevated

Additional diagnostic workup

- HbA1c
- Diagnostics for sepsis, e.g.:
  - CBC with differential
  - Serum lactate
- Diagnostics for myocardial infarction, e.g., 12-lead ECG
- Diagnostics for acute abdomen

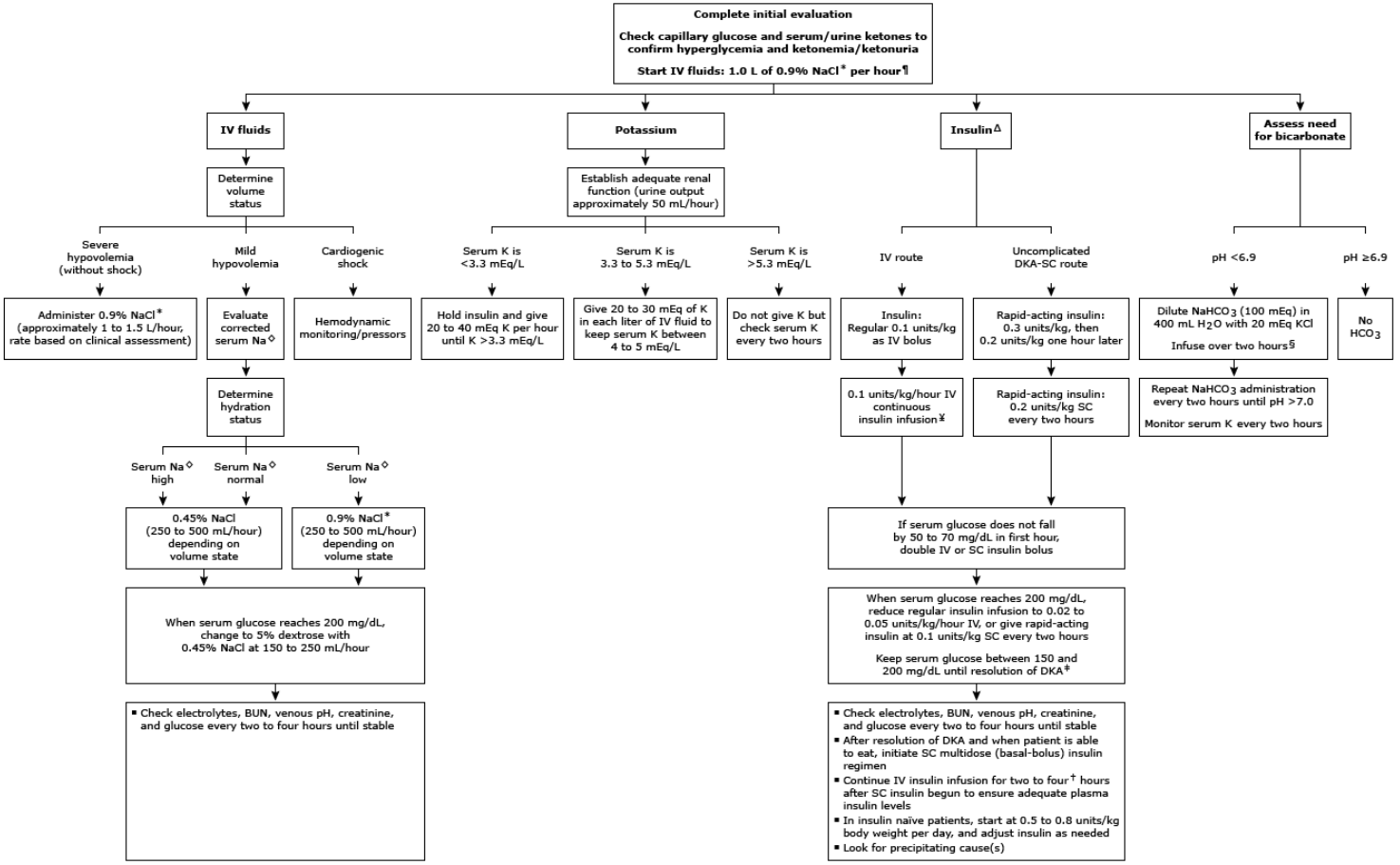
20.15 Indicators of severe diabetic ketoacidosis

- Blood ketones >6 mmol/L
- Bicarbonate <5 mmol/L
- Venous/arterial pH <7.0 (H^+ >100 nmol/L)
- Hypokalaemia on admission (<3.5 mmol/L)
- Glasgow Coma Scale score <12 (p. 194) or abnormal AVPU scale score (p. 188)
- O_2 saturation <92% on air
- Systolic blood pressure <90 mmHg
- Heart rate >100 or <60 beats per minute
- Anion gap >16 mmol/L

Severity of DKA [2]

	Arterial pH	Serum bicarbonate	Anion gap	Mental status
Mild	> 7.24	15–18 mEq/L	> 10 mEq/L	Alert
Moderate	7.0–7.24	10–15 mEq/L	> 12 mEq/L	Alert or drowsy
Severe	< 7.0	< 10 mEq/L	> 12 mEq/L	Stuporous

Treatment of diabetic ketoacidosis in adults



DKA diagnostic criteria: Serum glucose >250 mg/dL, arterial pH <7.3, serum bicarbonate <18 mEq/L, and at least moderate ketonuria or ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.

BUN: blood urea nitrogen; DKA: diabetic ketoacidosis; H_2O: water; HCO_3: bicarbonate; IV: intravenous; K: potassium; KCl: potassium chloride; Na: sodium; NaCl: sodium chloride; $NaHCO_3$: sodium bicarbonate; SC: subcutaneous.

* Isotonic buffered crystalloid (eg, Lactated Ringer) is a reasonable alternative.

¶ After history and physical examination, obtain capillary glucose and serum or urine ketones. Begin 1 L of 0.9% NaCl (or buffered crystalloid) over 1 hour, and draw arterial blood gas (or mixed venous blood gas), complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT. Obtain electrocardiogram and, if needed, chest radiograph and specimens for bacterial cultures.

Δ If initial serum K is <3.3 mEq/L, hold insulin and give KCl until K is >3.3 mEq/L.

◇ Serum Na^+ should be corrected for hyperglycemia (for each 100 mg/dL glucose >100 mg/dL, add 2 mEq to sodium value for corrected serum sodium value).

§ 100 mmol $NaHCO_3$ = 100 mEq $NaHCO_3$.

¥ An alternative IV insulin regimen is to give a continuous IV infusion of regular insulin at 0.14 units/kg/hour; at this dose, an initial IV bolus is not necessary.

‡ Please refer to the UpToDate topic on DKA for the definition of DKA resolution.

† This is an UpToDate clinical suggestion.

Diabetic ketoacidosis in adults: Rapid overview of emergency management

Clinical features
DKA usually evolves rapidly over a 24-hour period.
The earliest symptoms of marked hyperglycemia are polyuria, polydipsia, and weight loss. Common, early signs of ketoacidosis include nausea, vomiting, abdominal pain, and hyperventilation.
As hyperglycemia worsens, neurologic symptoms appear and may progress to include lethargy, focal deficits, obtundation, seizure, and coma.
Common causes of DKA include: infection; noncompliance, inappropriate adjustment, or cessation of insulin; new-onset diabetes mellitus; and myocardial ischemia.
Evaluation and laboratory findings
Assess vital signs, cardiorespiratory status, and mental status.
Assess volume status: vital signs, skin turgor, mucosa, urine output.
Obtain the following studies: serum glucose, urinalysis and urine ketones, serum electrolytes, BUN and creatinine, plasma osmolality, mixed venous blood gas, electrocardiogram; add serum ketones if urine ketones present.
DKA is characterized by hyperglycemia, an elevated anion gap* metabolic acidosis, and ketonemia. Dehydration and potassium deficits are often severe.
Serum glucose is usually greater than 250 mg/dL (13.9 mmol/L) and less than 800 mg/dL (44.4 mmol/L). In certain instances (eg, insulin given prior to emergency department arrival), the glucose may be only mildly elevated.
Additional testing is obtained based on clinical circumstances and may include: blood or urine cultures, lipase, chest radiograph.
Management
Stabilize the patient's airway, breathing, and circulation.
Obtain large bore IV (≥16 gauge) access; monitor using a cardiac monitor, capnography, and pulse oximetry.
Monitor serum glucose hourly, and basic electrolytes and venous pH or bicarbonate every two to four hours until the patient is stable.
Determine and treat any underlying cause of DKA (eg, pneumonia or urinary infection, myocardial ischemia).
Replete ECF volume and free water deficits:
▪ Give several liters of IV isotonic (0.9%) saline as rapidly as possible to patients with signs of shock.
▪ Give IV isotonic (0.9%) saline at 15 to 20 mL/kg per hour (ie, 1 to 1.5 L per hour for an average-sized adult), in the absence of cardiac compromise, for the first few hours to hypovolemic patients without shock.
▪ After intravascular volume is restored, give one-half isotonic (0.45%) saline at 4 to 14 mL/kg per hour if the corrected serum Na+¶ is normal or elevated; isotonic saline is continued if the corrected serum Na+¶ is reduced.
▪ Add dextrose to the saline solution when the serum glucose reaches ~200 mg/dL (11.1 mmol/L).
Replete potassium (K+) deficits:
▪ Regardless of the initial measured serum K+, patients with DKA have a large total body K+ deficit.
▪ Manage replacement based on initial serum K+ value:
◦ <3.3 mEq/L – Hold insulin and give potassium chloride 20 to 40 mEq/hour IV until K+ concentration is above 3.3 mEq/L; rarely, additional potassium supplementation may be necessary to avoid life-threatening muscle weakness and cardiac arrhythmias.
◦ 3.3 to 5.3 mEq/L – Give potassium chloride 20 to 30 mEq per liter IV fluid; maintain serum K+ between 4 to 5 mEq/L.
◦ >5.3 mEq/L – Do not give potassium; check serum K+ every 2 hours; delay administration of potassium chloride until serum K+ has fallen to 5 to 5.2 mEq/L.
Give insulin:
▪ For patients with K+ <3.3 mEq/L, do **not** give insulin; replete K+ and fluid deficit first.
▪ For patients with K+ ≥3.3 mEq/L, give regular insulin. Either of 2 regimens can be used: 0.1 units/kg IV bolus, then start a continuous IV infusion 0.1 units/kg per hour; **or** do not give bolus and start a continuous IV infusion at a rate of 0.14 units/kg per hour.
▪ If serum glucose does not fall by at least 50 to 70 mg/dL (2.8 to 3.9 mmol/L) in the first hour, double the rate of insulin infusion.
▪ When the serum glucose reaches 200 mg/dL (11.1 mmol/L), it may be possible to decrease the infusion rate to 0.02 to 0.05 units/kg per hour.
▪ Continue insulin infusion until ketoacidosis is resolved, serum glucose is below 200 mg/dL (11.1 mmol/L), and subcutaneous insulin is begun.
Give sodium bicarbonate to patients with pH below 6.90:
▪ If the arterial pH is below 6.90, give 100 mEq of sodium bicarbonate plus 20 mEq of potassium chloride in 400 mL sterile water over two hours; may be repeated if venous pH remains below 7.00.

DKA: diabetic ketoacidosis; BUN: blood urea nitrogen; IV: intravenous; ECF: extracellular fluid; Na: sodium; K: potassium.

* Patients with DKA usually present with a serum anion gap greater than 20 mEq/L (normal range approximately 3 to 10 mEq/L). However, the increase in anion gap is variable, being determined by several factors: the rate and duration of ketoacid production, the rate of metabolism of the ketoacids and their loss in the urine, and the volume of distribution of the ketoacid anions.

¶ Serum Na+ should be corrected for hyperglycemia; for each 100 mg/dL serum glucose exceeds 100 mg/dL (5.5 mmol/L), add 2 mEq to plasma Na+ for correction of Na+ value for hyperglycemia. A calculator to determine serum Na+ corrected for hyperglycemia is available separately in UpToDate.

Monitoring

- Hourly vitals and mental status and hydration status
- POC glucose every 1–2 hours until blood glucose < 250 mg/dL and hourly blood glucose readings are stable for at least 3 hours; then decrease monitoring to every 2–4 hours
- Serum osmolality every 1–4 hours
- Blood gas and BMP with electrolytes every 2–4 hours

Problems of Management

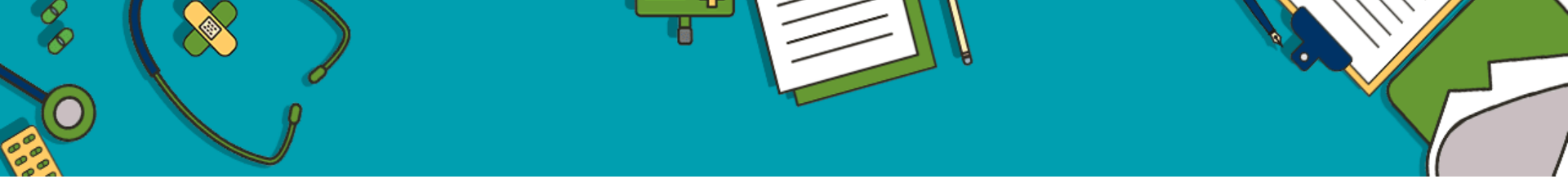
- **Cerebral edema**: excessive rehydration and hypertonic fluids may cause it.
- **Hypoglycemia**.
- **Hypokalemia** from potassium loss in the urine.
- **Pulmonary edema** from excessive fluid replacement.

Prognosis

- IV glucose and insulin are continued until patient feels able to eat without vomiting.
- Then changed into injection regimen.
- Mortality of DKA is around 5% and increased in elderly.
- Must advice patients as to how to avoid recurrence.

Hyperosmolar Hyperglycemic Nonketotic Syndrome (HHNS)

Comparison of DKA and HHS		
	Diabetic ketoacidosis	**Hyperosmolar hyperglycemic state**
Insulin	• Absent	• Present
Ketones	• Present	• Absent
Pathogenesis	• Acute stress (e.g., infection) → increased metabolic demand or insulin noncompliance → ↑ lipolysis → ↑ fatty acids → ↑ ketogenesis (β-hydroxybutyrate > acetoacetate)	• Severe hyperglycemia → ↑ serum osmolality → osmotic diuresis → dehydration • Especially the elderly are more susceptible to dehydration than younger people
Signs/symptoms	• Dehydration • Delirium/psychosis • Kussmaul breathing • Abdominal pain • Nausea, vomiting • Fruity (acetone) breath odor	• Profound dehydration • Polydipsia • Polyuria • Lethargy • Focal neurological deficits • Seizures
Labs	• Hyperglycemia • Anion gap metabolic acidosis (↑ H^+, ↓ HCO_3) • Decreased intracellular K^+ (normal or increased serum K^+) • Hyperkaliuria (total K^+ depletion) • Hyperketonuria, hyperketonemia • Leukocytosis	• Hyperglycemia (> 600 mg/dl) • ↑ Serum osmolality (> 320 mOsm/kg) • Decreased intracellular K^+ (normal or increased serum K^+) • Normal serum pH and ketones
Complications	• Cerebral edema • Cardiac arrhythmias • Heart failure • Mucormycosis (life-threatening)	• Coma • Death (if untreated)
Treatment	• Fluid resuscitation • Short-acting IV insulin • Replacement of potassium • Glucose supplementation in the case of hypoglycemia	• Fluid resuscitation • IV insulin • Replacement of potassium



HHNS: Overview

- A condition primarily seen in type II diabetics and the elderly due to extreme hyperglycaemia. Manifests with polyuria, polydipsia, nausea, vomiting, volume depletion (e.g., dry oral mucosa, decreased skin turgor), and eventually mental status changes, and coma. Unlike in DKA, there is some insulin available to suppress fat breakdown so ketosis does not result. Rather, severe hyperglycaemia (greater than 600 mg/dL) may develop. Treatment consists of IV insulin electrolyte and fluid replacement.

- Usually caused by ingestion of glucose-rich fluids, medications (thiazide, steroids), and illness (infection, MI).

Clinical Features

- Thirst, polyuria
- Signs of extreme dehydration and volume depletion (hypotension and tachycardia)
- CNS findings and focal neurologic signs are common (seizures, Impairment of the LOC – 2ry to hyperosmolarity).
- Lethargy and confusion may develop, leading to convulsions and coma
- Evidence of underlying illness (pneumonia, UTI).

Diagnosis and Labs

- Hyperglycaemia >600 mg/dL
- Increased serum osmolality >320 mOsm/kg.
- Decreased intracellular K+ (normal or increased serum K+).
- Serum pH >7.3. (no acidosis)
- Serum HCO3 >15mEq/L.
- No Ketones

Management

The main goals in HHNS treatment are:

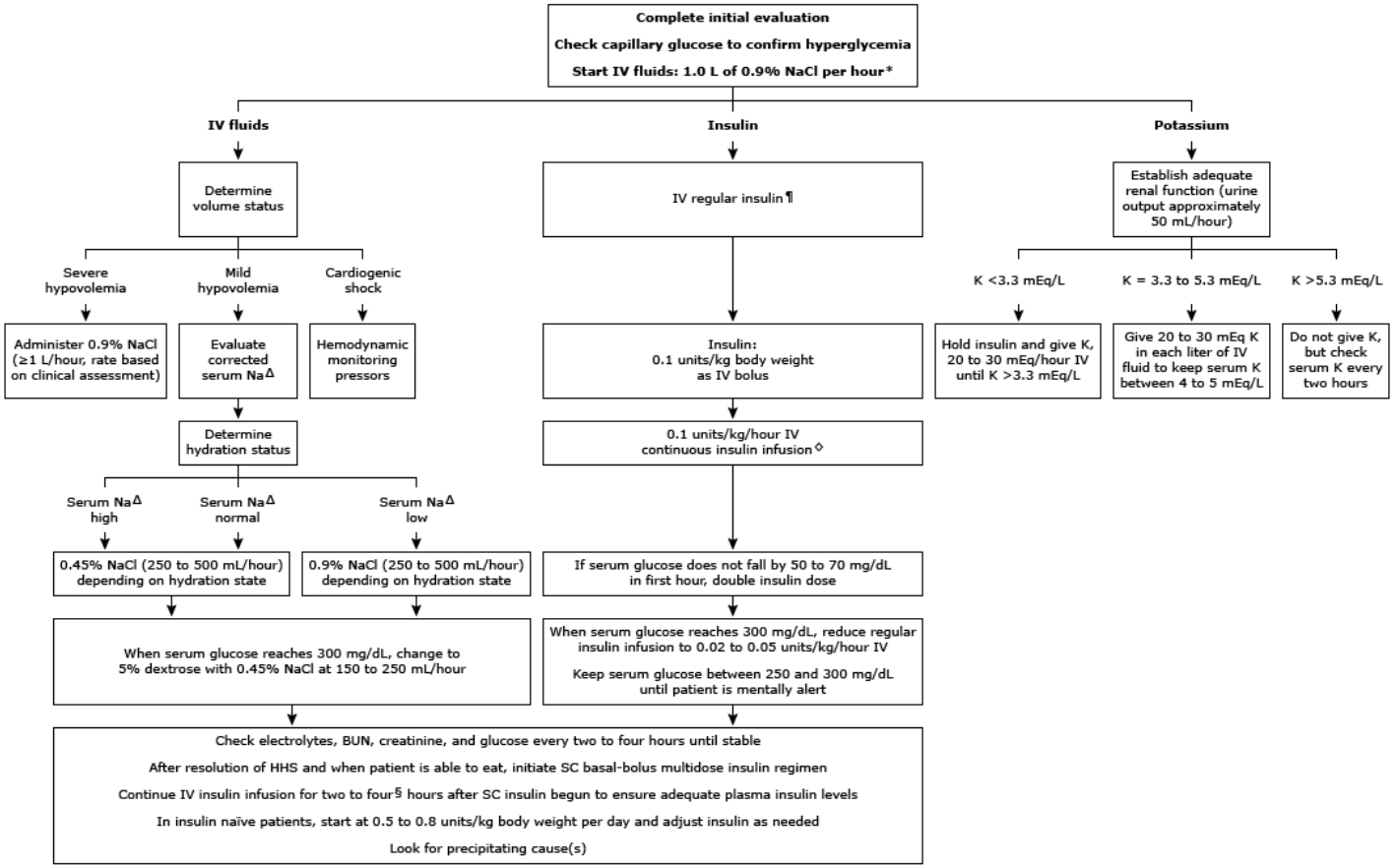
- To vigourously rehydrate the patient while maintaining electrolyte haemostasis
- To correct hyperglycaemia
- To treat underlying diseases
- To monitor and assist, cardiovascular, renal and CNS function

A) Fluid replacement

B) IV insulin

C) replacement of K+

Treatment of hyperosmolar hyperglycemic state in adults



HHS diagnostic criteria: Serum glucose >600 mg/dL, arterial pH >7.3, serum bicarbonate >15 mEq/L, and minimal ketonuria and ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.

HHS: hyperosmolar hyperglycemic state; IV: intravenous; NaCl: sodium chloride; K: potassium; Na: sodium; BUN: blood urea nitrogen; SC: subcutaneous.

* After history and physical exam, obtain capillary glucose and serum or urine ketones (nitroprusside method). Begin 1 liter of 0.9% NaCl over one hour, and draw arterial blood gases, complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT. Obtain electrocardiogram, chest radiograph, and specimens for bacterial cultures, as needed.

¶ If initial serum K is < 3.3 mEq/L, hold insulin and give potassium chloride until K is >3.3 mEq/L.

Δ Serum Na^+ should be corrected for hyperglycemia (for each 100 mg/dL glucose >100 mg/dL, add 2.0 mEq to sodium value for corrected serum sodium value).

◇ An alternative IV insulin regimen is to give a continuous intravenous infusion of regular insulin at 0.14 units/kg per hour; at this dose, an initial intravenous bolus is not necessary.

§ This is an UpToDate clinical suggestion.

Prognosis

Higher mortality rate than DKA (20-30%)

Poor prognostic factors include:

- Hypothermia
- Hypotension (systolic blood pressure <90 mmHg)
- Tachy or bradycardia
- Severe hypernatraemia (sodium 160 mmol/L)
- Serum osmolality >360 mOsm/kg)
- The presence of other serious comorbidities

Complications

- Thromboembolic events (MI, mesenteric thrombosis, pulmonary embolism, and disseminated intravascular coagulation)
- Cerebral oedema
- Adult respiratory distress syndrome
- Rhabdomyolysis
- Coma and death

Hypoglycemia

Definition

- In diabetic patients it is defined as all episode of an abnormally low plasma glucose concentration (with or without symptoms) that expose the individual to harm

- blood glucose < 3.5 mmol/L (63 mg/dL) in a person with diabetes.

Hypoglycaemia

- is more common among patients with type 1 diabetes than those with type 2 diabetes and is usually limited to patients with type 2 diabetes treated with specific medication classes (eg, **insulin, sulfonylureas, or meglitinides**).

Causes

- Hypoglycemia is the result of the interplay between absolute or relative therapeutic insulin excess and compromised physiologic and behavioral defenses against falling plasma glucose concentrations (**defective glucose counterregulation** and **impaired awareness of hypoglycemia)**

Glucose counter regulation in healthy individuals

1. endogenous **insulin** release from pancreatic β cells is suppressed (first line of defense)
2. release of **glucagon** from pancreatic α cells is increased
3. the autonomic nervous system is activated, with release of **catecholamines** (epinephrine) both systemically and within the tissues.
4. In addition, stress hormones, such as cortisol and growth hormone, are increased in the blood, they limit glucose utilization and enhance hepatic glucose production – they contributing only if hypoglycemia persists for several hours.

Counterregulatory response to hypoglycemia

Condition	Glucose	Insulin	Glucagon	Epinephrine	Autonomic symptom response
No diabetes	↓	Decreases	Increases	Increases	Activated
T1DM	↓	No decrease*	No increase*	Attenuated increase*¶	Attenuated activation or absent¶
T2DM					
Early	↓	Decreases	Increases	Increases	Activated
Late (absolute endogenous insulin deficiency)	↓	No decrease*	No increase*	Attenuated increase*¶	Attenuated activation or absent¶

Iatrogenic hypoglycemia is the result of the interplay of absolute or relative therapeutic insulin excess and compromised physiologic and behavioral defenses against falling plasma glucose concentrations in type 1 diabetes mellitus (T1DM) and advanced type 2 diabetes mellitus (T2DM).

Impaired awareness of glucose

- Individuals with type 1 diabetes may have reduced (impaired) awareness of hypoglycaemia. Symptoms can be experienced less intensely, or even be absent.
- That is because with longer duration of disease and in response to frequent hypoglycaemia episodes , **the threshold for symptoms shifts to a lower glucose concentration**.
- it affects ~20–25% of people with type 1 diabetes and < 10% with insulin-treated type2 diabetes.

Risk factors & other causes

11.8 Hypoglycaemia: common causes and risk factors

Causes of hypoglycaemia

- Missed/delayed meal
- Unexpected or unusual exercise
- Alcohol
- Error in oral hypoglycaemic or insulin dose/timing
- Lipohypertrophy causing variable insulin absorption
- Gastroparesis due to autonomic neuropathy
- Malabsorption, e.g. coeliac disease
- Unrecognised other endocrine disorder, e.g. Addison's disease
- Factitious (deliberately induced)
- Breastfeeding

Risk factors for severe hypoglycaemia

- Strict glycaemic control
- Impaired awareness of hypoglycaemia
- Extremes of age
- Long duration of diabetes
- History of previous hypoglycaemia
- Renal impairment

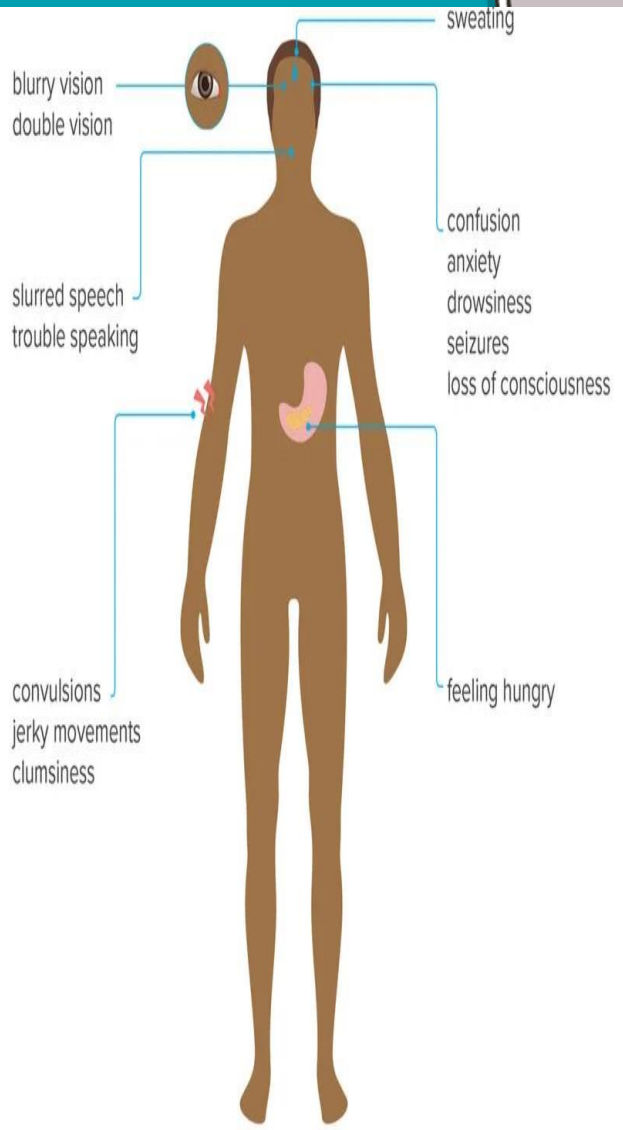
Symptoms

- **Hypoglycemia causes neurogenic (autonomic) and neuroglycopenic symptoms.**
- **Neurogenic symptoms**

Due to due to sympathetic neural activation and epinephrine release

& Include tremor, palpitations, and anxiety/arousal and sweating,

hunger, and paresthesias



Cont.

- **The neuroglycopenic symptoms**

Due to direct effects of glucose deprivation on the central nervous system

& Include dizziness, weakness, drowsiness, delirium, confusion, and, at lower plasma glucose concentrations, seizure and coma

- **Hypoglycaemia also affects mood**, inducing a state of increased tension and low energy

- The plasma glucose level at which the onset of symptoms of hypoglycemia occurs, varies between individuals.

Clinical classification

- **Documented symptomatic hypoglycemia** an event during which typical symptoms of hypoglycemia are accompanied by a measured glucose level <70 mg/dL (3.9 mmol/L).

- **Asymptomatic hypoglycemia** an event not accompanied by typical symptoms of hypoglycemia but with a measured glucose level <70 mg/dL (3.9 mmol/L).

- **Probable symptomatic hypoglycemia** an event during which typical symptoms of hypoglycemia are not accompanied by measurement of the glucose level but resolve after action taken to reverse hypoglycemia.
- **Pseudohypoglycemia** an event during which the person with diabetes reports typical symptoms of hypoglycemia but has a measured glucose level ≥70 mg/dL (3.9 mmol/L).

Health-related outcomes

It lowers the quality of life in patients and is associated with many health realted outcomes:

- Mortality and cardiovascular disease
- Cognitive impairment and dementia
- Falls and fractures

Management

prevention

treating

Depends on severity and whether the patient is conscious

- **Mild hypoglycemia**

*early, oral fast-acting carbohydrate, with repeating the measurement within 15-60 mins. Repeat fast-acting if still hypoglycemic.

*followed by a complex carbohydrate snack (long acting). This is sufficient

- **Severe hypoglycemia**

Patient is semi/unconscious

*IV access: IV glucose (25g of 50% dextrose)

*Without IV access: administration of glucagon (subcutaneous, intramuscular, or nasal) which will usually lead to recovery of consciousness within approximately 15 minutes.

- Full recovery may not occur immediately and reversal of cognitive impairment may take 60 mins.
- fail to regain consciousness after blood glucose levels are back to normal? cerebral edema


Thank
You