DM and its complication

Summary

Diabetes mellitus (DM) describes a group of metabolic diseases that are characterized by chronic hyperglycemia. Type 1 diabetes mellitus (T1DM) is the result of an autoimmune response that triggers the destruction of insulin-producing β cells in the pancreas and results in an absolute insulin deficiency. It often develops during childhood, manifesting with an acute onset (e.g., diabetic ketoacidosis). Type 2 diabetes mellitus (T2DM), which is much more common, has a strong genetic component as well as a significant association with obesity and a sedentary lifestyle. T2DM is characterized by insulin resistance and impaired insulin secretion due to pancreatic β-cell dysfunction, resulting in relative insulin deficiency. This type of diabetes usually remains undiagnosed for many years. Testing for hyperglycemia is recommended for patients with classic symptoms of diabetes mellitus, and screening is recommended for asymptomatic patients who are at high risk of prediabetes or diabetes (e.g., patients with obesity and additional risk factors). The diagnosis is made based on blood glucose or HbA1c levels. The main goal of treatment is blood glucose control tailored to glucose targets while avoiding hypoglycemia. Diabetes care should be comprehensive and patient-centered, and it should include monitoring and management of ASCVD risk factors, microvascular complications (e.g., diabetic retinopathy, diabetic nephropathy, diabetic neuropathy), and macrovascular complications (e.g., CAD, stroke, PAD). Management should also include general lifestyle modifications (e.g., smoking cessation, exercise, nutritional support) and pharmacotherapy (e.g., antihyperglycemics, statins, ACE inhibitors or angiotensin receptor blockers, and aspirin). The management of diabetes in children is largely similar to adults, except certain medications (sulfonylureas, dipeptidyl peptidase-4 inhibitors, SGLT-2 inhibitors, and thiazolidinediones) are not licensed for use in this age group.

Classification according to the WHO and American Diabetes Association (ADA)

[10][14]

- **Type 1**: formerly known as insulin-dependent (IDDM) or juvenile-onset diabetes mellitus
  - Autoimmune (type 1A)
  - **LADA**: Latent autoimmune diabetes in adults, a variant of diabetes characterized by a late onset of type 1 (autoimmune) diabetes that is often mistaken for type 2 diabetes.
  - Idiopathic (type 1B)
- **Type 2**: formerly known as non-insulin-dependent (NIDDM) or adult-onset diabetes mellitus
- **Gestational diabetes**
- **Other types of diabetes mellitus**
  - **MODY** (maturity-onset diabetes of the young): genetic defects leading to β-cell dysfunction
    - Different forms of autosomal dominant inherited diabetes mellitus that manifest before the age of 25 years and are not associated with obesity or autoantibodies
    - Multiple monogenic subtypes (most common: MODY II due to glucokinase gene defect, and MODY III, due to **hepatocyte nuclear factor**-1-α gene defect)
    - MODY II
      - A single mutation leads to impaired insulin secretion due to altered glucokinase function.
      - Glucokinase is the glucose sensor of the β cell, facilitating storage of glucose in the liver, especially at high concentrations.
      - There is no increased risk of microvascular disease.
      - Despite stable hyperglycemia and chronically elevated HbA_{1C} levels, MODY II can be managed with diet alone.
    - All other subtypes, including MODY III, require medical treatment either with insulin or sulfonylureas.
  - **Pancreatogenic diabetes mellitus**: following pancreatectomy and due to conditions that lead to destruction of pancreatic endocrine islets (e.g., hemochromatosis, cystic fibrosis)
  - Endocrinopathies: Cushing disease, acromegaly
  - Drug-induced diabetes, e.g., due to corticosteroids (steroid diabetes)
  - Genetic defects affecting insulin synthesis
  - Infections (e.g., congenital rubella infection)
  - Rare immunological diseases: stiff person syndrome
  - Other genetic syndromes that are associated with diabetes mellitus (e.g., Down syndrome)

- Definition/Etiology:

- Diabetes mellitus (DM) is a disorder of carbohydrate metabolism, caused by relative or absolute deficiency of insulin, hyperglycemia, and end-organ complications (nephropathy, retinopathy, neuropathy, accelerated atherosclerosis).

A. Type 1 DM (insulin-dependent or juvenile onset):

- Accounts for 5-10% of diabetes worldwide.
- The age of onset is usually age <30 (Onset in childhood).
- There is an increased prevalence of autoantibodies to islet cells (Insulin dependent from an early age).
- Not related to obesity. Patients usually have a lean body build and are prone to ketosis owing to absent insulin production.

B. Type 2 DM (non-insulin-dependent or maturity onset)

- It is the most common type of diabetes, accounting for 90% of cases.
- Age of onset is usually age 40 (Onset in adulthood).
- Directly related to obesity
- Defined as insulin resistance.

Diabetes mellitus (DM) is characterized by hyperglycemia and glycosuria and is an end-point of a few disease processes (Table 171.1). The most common type occurring in childhood is type 1 DM (T1D), which is caused by autoimmune destruction of the insulin-producing β cells (islets) of the pancreas, leading to permanent insulin deficiency. Type 2 DM (T2D) results from insulin resistance and relative insulin deficiency usually in the context of exogenous obesity. The incidence of T1D and T2D in the United States is increasing. Less common types of diabetes result from genetic defects of the insulin receptor or inherited abnormalities in sensing of ambient glucose concentration by pancreatic β cells (see Table 171.1).

Type 1 vs Type 2 diabetes mellitus

Features	Type 1 DM	Type 2 DM [1]
Genetics	• Positive HLA-DR4 and HLA-DR3 association • Weak familial predisposition [2] • Polygenic	• Negative HLA association • Strong familial predisposition [3] • Polygenic
Pathogenesis	• Autoimmune destruction of β cells → absolute insulin deficiency	• Insulin resistance, progressive destruction of pancreatic β-cells
Association with obesity	• No	• Yes
Onset	• Childhood onset typically < 20 years but can occur at any age • Peaks at age **4–6 years** and **10–14 years**	• Gradual; usually at age > 40 years
C-peptide (insulin)	• Decreased or absent	• Initially elevated, decreased in advanced stage
Glucose intolerance	• Severe	• Mild to moderate
Insulin sensitivity	• High	• Low
Risk of ketoacidosis	• High	• Low
β-cells in the islets	• Decreased	• Variable (with amyloid deposits)
Classic symptoms (i.e., polyuria, polydipsia, polyphagia, weight loss)	• Common	• Sometimes
Histology	• Leukocyte infiltration of islets	• Amyloid polypeptide (IAPP) deposits in islets
Treatment	• Insulin therapy	• Lifestyle changes • Oral antidiabetic drugs • Insulin therapy

TypeI DM:

Etiology:

A. **Etiology.** Type 1 DM is an **autoimmune disease** due to genetic and environmental factors.

1. **Genetic factors**
   a. There are strong genetic influences, but inheritance has not been found to fit into classic Mendelian patterns (autosomal or X-linked). Polymorphisms in human leukocyte antigens (HLAs) (specifically DR3 and DR4 haplotypes) on chromosome 6 are responsible for most of the genetic risk in large genome-wide association studies. HLA is responsible for antigen presentation.
   b. Monozygotic twins have a >50% concordance rate, whereas dizygotic twins have only a 30% concordance rate. First-degree relatives of a patient with type 1 DM have 10-fold higher rate of developing type 1 DM.
2. **Environmental triggers**. Viral infections including enteroviruses (coxsackie) and rubella have been implicated but not definitely proven.
3. **Autoimmune factors**
   a. *Autoantibodies against islet antigens* (GAD65, ICA512, insulin, and ZnT8) are present in ~**85% of patients.**
   b. **Autoantibodies** may be detected in asymptomatic patients years before the onset of clinical symptoms. Screening of family members of patients with type 1 DM through national screening programs is encouraged.

Pathophysiology:

Pathophysiology

Normal insulin physiology [15]

- **Secretion**: Insulin is synthesized in the **β cells** of the **islets of Langerhans**. The cleavage of proinsulin (precursor molecule of insulin) produces **C-peptide** (connecting peptide) and insulin, which consists of two peptide chains (A and B chains).
- **Action**: Insulin is an anabolic hormone with a variety of metabolic effects on the body, primarily contributing to the generation of energy reserves (cellular uptake and metabolism of nutrients) and glycemic control.
  - Carbohydrate metabolism: insulin is the only hormone in the body that directly lowers the blood glucose level.
  - Protein metabolism: insulin inhibits proteolysis, stimulates protein synthesis, and stimulates cellular uptake of amino acids
  - Lipid metabolism: maintains a fat depot and has an antiketogenic effect
  - Electrolyte regulation: stimulates **intracellular potassium accumulation**

Type 1 diabetes [6]

- **Genetic susceptibility** and **environmental triggers** (often associated with previous viral infection) → **autoimmune response** with production of autoantibodies, e.g., anti-glutamic acid decarboxylase antibody (**anti-GAD**), anti-islet cell cytoplasmic antibody (**anti-ICA**) → progressive destruction of β cells in the pancreatic islets → **absolute insulin deficiency** → decreased glucose uptake in the tissues

Insulin deficiency result in disturbance of carbohydrate, fat & protein metabolism.
1- Fat metabolism: ↓ Lipogenesis → ↑ free fatty acids (FFA) →↑ Ketone bodies.
2- Carbohydrate metabolism:
- Hyperglycaemia due to - ↓ glucose uptake & utilization by the cells
- ↑ gluconeogenesis & glycogenolysis
- Hyperglycaemia leads to osmotic diuresis → polyuria & polydipsia
3- Protein metabolism: ↑ proteolysis → ↓ body wteight.

- Pathophysiology—low insulin **catabolic state**
  - Hyperglycemia → osmotic diuresis; when renal threshold for glucose reabsorption is reached (180 mg/dL) → glycosuria
  - Loss of fluid, electrolytes, calories, and dehydration
  - Accelerated lipolysis and impaired lipid synthesis → increased free fatty acids → ketone bodies → metabolic acidosis and Kussmaul respiration → decreased consciousness

Clinical picture:

Clinical picture

Common presentations	Insidious
• Polyuria, polydipsia, polyphagia & weight loss. • Diabetic keto-acidosis (DKA). • Secondary nocturnal enuresis	• Lethargy & abdominal pain. • Recurrent infections.

B. **Clinical features**

1. The **classic presentation** includes several weeks of **polyuria, polydipsia, nocturia,** and occasionally enuresis. As symptoms progress, weight loss, vomiting, and dehydration occur.
2. **Diabetic ketoacidosis (DKA)** may be the **initial presentation in 25% of patients** [see section VIII]. The younger the patient, the shorter the course of symptoms before DKA occurs.
3. Girls may present with candidal vulvovaginitis.

Onset	• Often sudden • **Diabetic ketoacidosis** (DKA) is the first manifestation in 25–50% of cases [10] • Children may present with acute illness and classic symptoms • A thin appearance is typical for patients with T1DM.
Clinical features	• **Classic symptoms of hyperglycemia** ◦ **Polyuria**, which can lead to secondary enuresis and nocturia in children ◦ **Polydipsia** ◦ **Polyphagia** • Nonspecific symptoms ◦ Unexplained weight loss ◦ Visual disturbances, e.g., blurred vision ◦ Fatigue ◦ Pruritus ◦ Poor wound healing ◦ Increased susceptibility to infections ◦ Calf cramps [21]

Diabetes mellitus should be suspected in patients with recurrent cellulitis, candidiasis, dermatophyte infections, gangrene, pneumonia (particularly tuberculosis reactivation), influenza, genitourinary infections (UTIs), osteomyelitis, and/or vascular dementia.

Clinical Diagnosis:

A **diagnosis** of DM is made based on four glucose abnormalities that may need to be confirmed by repeat testing: (1) Fasting serum glucose concentration ≥126 mg/dL, (2) a random venous plasma glucose ≥200 mg/dL with symptoms of hyperglycemia, (3) an abnormal oral glucose tolerance test (OGTT) with a 2-hour postprandial serum glucose concentration ≥200 mg/dL, and (4) a HgbA1c ≥6.5%.

A patient is considered to have **impaired fasting glucose** if fasting serum glucose concentration is 100-125 mg/dL or **impaired glucose tolerance** if 2-hour plasma glucose following an OGTT is 140-199 mg/dL. Sporadic hyperglycemia can occur in children, usually in the setting of an intercurrent illness. When the hyperglycemic episode is clearly related to an illness or other physiological stress, the probability of incipient diabetes is small (<5%).

Interpretation of hyperglycemia tests [10]

	FPG	2-hour glucose value after OGTT	HbA1c
Diabetes mellitus	**≥ 126 mg/dL** (≥ 7.0 mmol/L)	**≥ 200 mg/dL** (≥ 11.1 mmol/L)	**≥ 6.5%**
Prediabetes	100–125 mg/dL (5.6–6.9 mmol/L) = **impaired fasting glucose**	140–199 mg/dL (7.8–11.0 mmol/L) = **impaired glucose tolerance**	5.7–6.4%
Normal	< 100 mg/dL (< 5.6 mmol/L)	< 140 mg/dL (< 7.8 mmol/L)	< 5.7%

Additional recommended evaluation [27]

Perform in all patients as part of the initial diagnostic workup and reassess at least annually.

- BMP (Basic metabolic panel)
  - Renal function
  - Electrolytes, including potassium
- Spot urinary albumin-to-creatinine ratio: to detect microalbuminuria
- CBC with platelets
- Liver chemistries
- Lipid panel
- Additionally consider: [27]
  - Patients with suspected or confirmed T1DM: TSH
  - Patients on metformin: vitamin B12 level
  - Select patients: calcium, phosphorous, vitamin D level

Additional optional studies

These tests are not routinely indicated or required to establish a diagnosis.

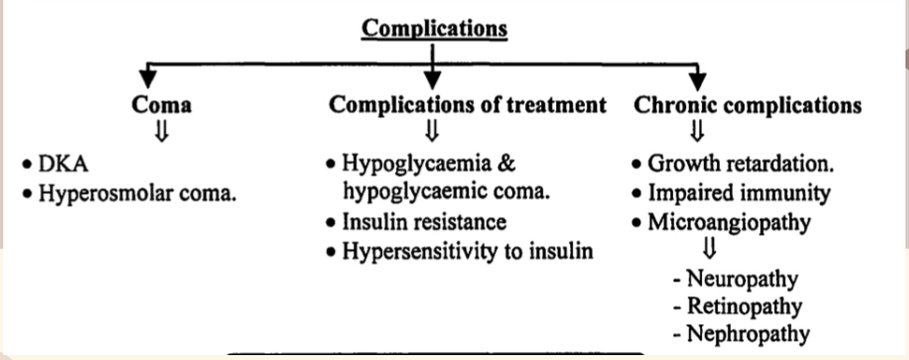
- **C-peptide**: can help differentiate between types of diabetes [28][29]
  - ↑ C-peptide levels may indicate insulin resistance and hyperinsulinemia → T2DM
  - ↓ C-peptide levels indicate an absolute insulin deficiency → T1DM
- **Urinalysis**
  - Glucosuria may be present if the renal threshold for glucose is reached (nonspecific for diabetes mellitus).
  - Ketone bodies: positive in acute metabolic decompensation (diabetic ketoacidosis) [29]
  - Microalbuminuria: early sign of diabetic nephropathy
- **Islet autoantibody testing**: Consider in patients with diagnosed diabetes mellitus if there is clinical suspicion for T1DM. [10]
  - **Antiglutamic acid decarboxylase antibodies** (Anti-GAD): An antibody against the enzyme glutamic acid decarboxylase, which is responsible for the conversion of glutamic acid to GABA [29]
    - Positive result confirms T1DM
    - Negative result should trigger testing for other antibodies (e.g., anti-tyrosine phosphatase-related islet antigen 2 (IA-2), anti-zinc transporter 8 antibodies) and/or consultation with a specialist
  - Anti-tyrosine phosphatase-related islet antigen 2 (IA-2) [29]
  - Anti-zinc transporter 8 antibodies

> While screening for T1DM with autoantibodies is not routinely recommended, it can be considered for patients with first-degree relatives with T1DM or in the setting of research trials. [10]

> Consider specialist consultation if the differentiation between T2DM and T1DM is unclear.

Before we tlking about management, let's talk about complications:

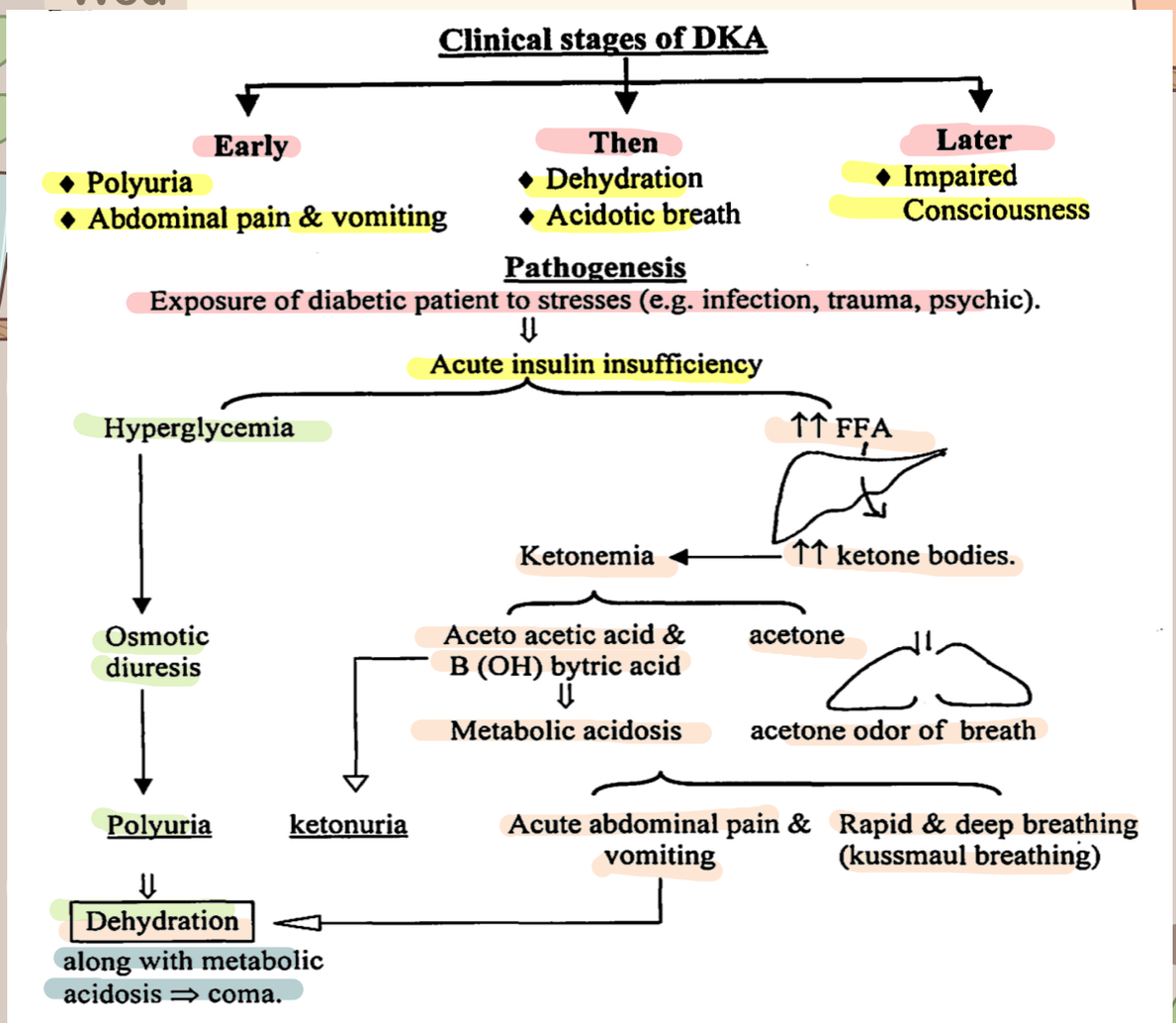
Complications:



First:Acute Complications:

A.Diabetic Ketoacidosis

If the clinical features of new-onset T1D are not detected, **diabetic ketoacidosis (DKA)** will occur. DKA may also occur in patients with known T1D if insulin injections are omitted or during an intercurrent illness when greater insulin requirements are unmet in the presence of elevated concentrations of the counter-regulatory and stress hormones (glucagon, growth hormone [GH], cortisol, and catecholamines). DKA can be considered to be present if (1) the arterial pH is below 7.3, (2) the serum bicarbonate level is below 15 mEq/L, and (3) ketones are elevated in serum or urine.



Pathogenesis:

Diabetic ketoacidosis (DKA)

DKA primarily affects patients with **type 1 diabetes**.

Osmotic diuresis and hypovolemia

- 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 → hyperglycemia → **hyperosmolality** → osmotic diuresis and loss of electrolytes → **hypovolemia**

> ⓘ Hypovolemia resulting from DKA can lead to acute kidney injury (AKI) due to decreased renal blood flow! Hypovolemic shock may also develop.

Metabolic acidosis with increased anion gap

- Insulin deficiency also **increases** fat breakdown (lipolysis).
- Metabolic acidosis develops as the free fatty acids generated by lipolysis become **ketones**, two of which are acidic (acetoacetic acid and beta-hydroxybutyric acid).
- Serum bicarbonate is consumed as a buffer for the acidic ketones. Metabolic acidosis with an elevated anion gap is therefore characteristic of DKA.
- Insulin deficiency → ↑ **lipolysis** → ↑ free fatty acids → **hepatic** ketone production (ketogenesis) → **ketosis** → bicarbonate consumption (as a buffer) → **anion gap metabolic acidosis**

> DKA is an important cause of anion gap metabolic acidosis with respiratory compensation.

Intracellular potassium deficit

- As a result of **hyperglycemic hyperosmolality**, potassium shifts along with water from inside cells to the extracellular space and is lost in the urine.
- Insulin normally promotes cellular potassium uptake but is absent in DKA, compounding the problem.
- A total body **potassium deficit** develops in the body, although serum potassium may be normal or even paradoxically elevated.
- Insulin deficiency → hyperosmolality → **K^+ shift out of cells** + lack of insulin to promote K^+ uptake → intracellular K^+ depleted → total body K^+ deficit despite normal or even elevated serum K^+

> There is a **total body potassium deficit in DKA**. This becomes important during treatment, when insulin replacement leads to rapid potassium uptake by depleted cells and patients may require potassium replacement.

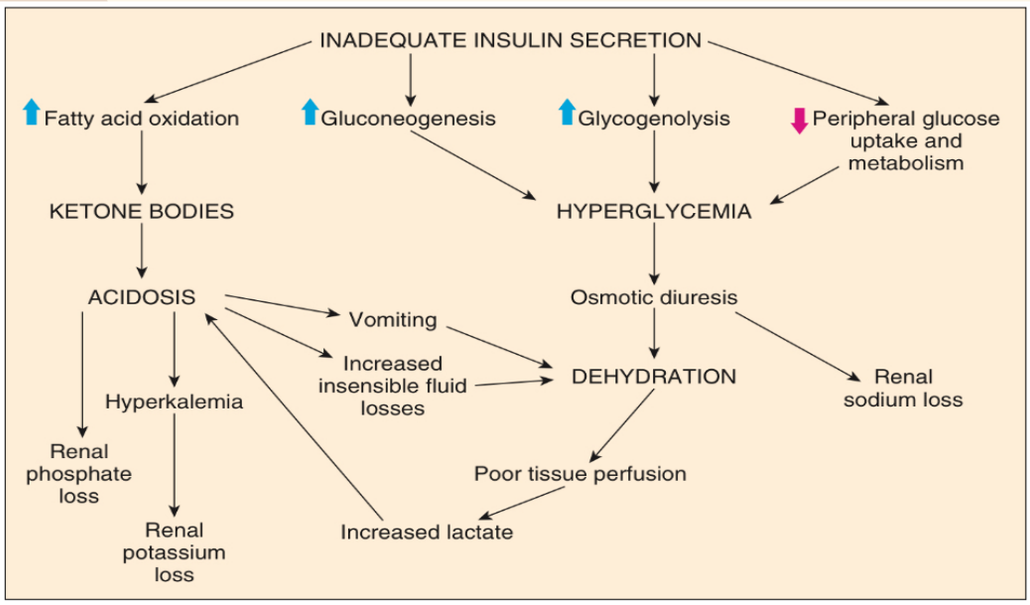


FIGURE 171.2 Pathophysiology of diabetic ketoacidosis.

To Sum Up:

- Although more common in those with Type 1 diabetes, diabetic ketoacidosis (DKA) can definitely present in those with Type 2 diabetes.

- DKA can be the initial presentation of DM, especially in patients lacking regular health follow-up.

- <u>Presentation:</u>

- DKA is often precipitated by infections, severe stress as myocardial infarction or omission of insulin.

- Insulin and glucagon normally act in opposition to one another, with insulin inhibiting glucagon release. Patients with DM (especially type I DM), however, are unable to synthesize sufficient insulin to prevent hyperglycemia and to inhibit glucagon's effects.

- Because glucose is inadequately transported into cells in patients with DM and DKA, the body perceives hypoglycemia and a starved state despite high serum glucose levels. Adrenergic nervous system activation and increased glucagon production result.

- Glucagon stimulates ketoacids synthesis in adipose tissue because during starvation ketoacids can be used by cells for energy in place of glucose.

- If ketones increase sufficiently in the blood, they can lead to ketoacidosis → metabolic acidosis.

- Increased alveolar ventilation partially compensates for the metabolic acidosis → ventilation becomes deep and rapid (Kussmaul breathing).

- Patients with DKA clinically exhibit nausea and vomiting, severe abdominal pain, dry mucous membranes and lethargy. There is classically a fruity odor on their breath (acetone odor).

- DKA patient has both clinical (polyuria, polydipsia, volume depletion) and biochemical (hyperglycemia, low bicarbonate, high anion gap) signs. Hyperglycemia is associated with glycosuria that leads to obligatory water loss and subsequent marked dehydration.
- Metabolic acidosis during diabetic ketoacidosis (DKA) is typically accompanied by hyperkalemia.

- DKA is characterized by an osmotic diuresis that reduces total body K stores even though the serum K level may be elevated. This hyperkalemia is sometimes called paradoxical, because the body potassium reserves are actually depleted due to increased gastrointestinal losses and osmotic diuresis.

- The main causes of this paradoxical hyperkalemia are:
  - Extracellular shift of potassium in exchange to hydrogen ion, with resultant intracellular potassium deficit.
  - Impaired insulin-dependent cell entry of the potassium ion.

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Laboratory studies reveal hyperglycemia (serum glucose concentrations ranging from 200 mg/dL to >1,000 mg/dL). Arterial pH is below 7.30, and the serum bicarbonate concentration is less than 15 mEq/L. Serum sodium concentrations may be elevated, normal, or low, depending on the balance of sodium and free water losses. The measured serum sodium concentration is artificially low, however, because of hyperglycemia. Hyperlipidemia also contributes to the decrease in measured serum sodium. The level of blood urea nitrogen (BUN) can be elevated with prerenal azotemia secondary to dehydration. The white blood cell count is usually elevated and can be left-shifted without implying the presence of infection. Fever is unusual and should prompt a search for infectious sources that may have triggered the episode of DKA.

1- Diagnostic

Diabetic	Keto	Acidosis
♦ Blood glucose > 300 mg/dl ♦ Glucosuria	♦ Ketonaemia Serum ketones > 3 m.mol/l ♦ Ketonuria	♦ Metabolic acidosis - pH < 7.25 - HCO_3 < 15 meq/L - ↓ $PaCo_2$

2- Others

- Serum electrolytes (Sodium and potassium)
- Sepsis workup if suspected(WBCs count, blood culture, urine culture)
- ECG for hypo or hyperkalemia.

Differential diagnosis

❶ from other cause of acute abdominal pain

❷ from other causes of metabolic acidosis:

- Renal failure
- Organic acidemias.
- Lactic acidosis with sepsis & shock
- Ingestions → Salcylates
  → Ethylene glycol
- Acute diarrhea
- Renal tubular acidosis

❸ From other causes of coma in diabetic child:

A. Hyperosmolar non ketotic coma (rare):

- Blood glucose > 800 mg /dl
- Serum osmolality > 350 m.osmol/L
- Severe dehydration
- No or slight ketones
- Acidosis is mainly due to lactic acidosis

B. Hypoglycemic coma:

- Known diabetic with insulin overdose or exercise or delayed meals
- Reactive sympathetic stimulation(↑catecholamines): Pallor , hunger pains, tachycardia, sweating ,jitterness, tremor, irritability
- Glucopenia of CNS : Lethargy, limpness , may be seizures.
- Blood glucose < 50 mg/dl (< 2.6 m mol /l)
- Rapid response to I.V. glucose

- Treatment:

- The most appropriate initial management is rapid, intravenous administration of normal saline and regular insulin.

- Essential measures in the management of DKA include the following:
  - Restoration of intravascular volume: using 0.9% saline (normal saline).
  - Correction of hyperglycemia: using intravenous regular insulin.
  - Correction of electrolyte abnormalities: Potassium correction is very crucial.
  - Correct the underlying cause: noncompliance with medications, infection, pregnancy, or any serious illness.

- Early potassium supplementation is very important in the treatment of patients with DKA. Treatment with insulin and intravenous fluids lead to a rapid decrease in serum potassium levels even if they are initially elevated. All hyperkalemic patients should start receiving potassium once the serum potassium level goes below 4.5 mEq/L. In patients with normal or low potassium levels, potassium replacement should be started with initiation of intravenous fluid therapy.

- The best markers indicating resolution of ketonemia are the serum anion gap and direct assay of beta-hydroxybutyrate (BH), which is the predominant ketone in DKA. The anion gap estimates the unmeasured anion concentration in the blood and returns to normal with the elimination of ketoacid anions. A rise in serum bicarbonate and arterial pH provides further confirmation of the improvement in acidosis.

Diabetic ketoacidosis	
Patient characteristics	• Young age • Brittle type 1 diabetes • May be initial manifestation of diabetes
Clinical symptoms	• Acute to subacute onset ○ **Initial**: Polydipsia/polyuria, blurred vision, weight loss ○ **Later**: Altered mentation, hyperventilation, abdominal pain
Diagnosis	• **Glucose 250-500 mg/dL** • Bicarbonate <18 mEq/L • Elevated anion gap • Positive serum ketones
Treatment	• High-flow IV fluids • IV insulin • Follow & replace potassium

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Management

A. Acidotic phase (in ICU)

Insert 2 i.v lines ; one for I.V fluids & the other for I.V insulin(*given simultaneously*)

1. Fluid therapy

a. Shock therapy : - Saline or lactated ringer
- 20 ml/kg over 1 hour.

b. In the 2nd hour and until resolution of DKA: **(Milwaukee protocol)**

* Deficit is given with maintenance and given over next 24 hour

* Amount = $\frac{\text{85 ml/kg + Maintenance-Bolus}}{\text{23 hours}}$

- Deficit :85 ml/kg
- Maintenance (24hr) = 100ml/kg(for the 1st 10 kg) + 50ml/kg (for the 2nd 10) + 25 ml/kg (for all remaining kg)

* Type of fluid:
- 0.45% NaCl plus 20 mEq/L K phosphate and 20 mEq/L K acetate
- When blood glucose reaches 250 mg/dl add glucose 5% to saline as 14 mmol/L.

* Precautions:
- Slow correction to avoid brain edema.
- Acidosis almost always corrected by fluids &insulin infusion so, Sodium bicarbonate is not usually indicated. It is given only in severe intractable acidosis unresponsive to other therapy (pH < 7.1)

2. Insulin therapy

* Use regular (crystalline) insulin as slow infusion **0.1** unit/kg/hour without bolus dose
* Decrease insulin infusion rate when the patient become conscious and blood glucose drop below 300 mg/dl to avoid hypoglycemia
* Shift to subcutaneous insulin (0.2- 0.4 u/kg every 6-8 hr) when:
- pH > 7.30
- HCO_3 > 16 meq/L
- Sodium is stable between 135-145 mEq/L.
- No vomiting.

3. Flow sheet: For electrolytes , blood glucose , pH ,and fluid balance every 1-4 hours.

4. Treat precipitating factors e.g. Antibiotics for infections.

Hazards during treatment:

* Hypokalemia. * Hypoglycemia. * Brain edema

B. Post acidotic phase

Regular Insulin	Diet
Dose: 0.2-0.4 u/kg/ 6-8 hrs; SC Given 0.5 -1 hr before meals	- Sips of water , skimmed milk, Dietetic juice. Two days later give average diet (limit fat & carbohydrate)

C. Life long management

1. Insulin

Dose:

- Prepubertal **0.7 unit/kg/day**
- Midpubertal **1.0 unit/kg/day**
- End of puberty **1.2 unit/kg/day**

Types:

- Short acting: - Regular insulin(Crystalline insulin, Humulin R)
  - Insulin Aspart (Novolog) /insulin Lispro (Humalog)
- Intermediate insulin(NPH, insulin Monotard , Humulin N)
- Long acting insulin(Glargine ; Lantus)

Regimens:

1. Two injections regimen:
   - 2/3 the total daily dose before breakfast
   - 1/3 the dose before evening meal
   * Each dose contain 1/3 rapid analog & 2/3 NPH(old method)
2. Three injection regimen:
   - NPH and rapid acting analog bolus at breakfast
   - Rapid acting analog bolus at supper
   - NPH at bed time
3. Multiple dose injections (recent ,very effective but expensive):
   - Use Glargine as basal insulin and premeals boluses of short acting analogs as Insulin Aspart (A) or Insulin Lispro (L)
   - Galrgine dose should be 25-30% of total insulin dose in toddlers and 40-50% in older children
   - The remaining part of insulin dose is divided evenly as 3 premeal boluses of insulin Aspart or Lispro
4. Continuous subcutaneous insulin infusion using automated insulin pump (recent)
5. Once daily long acting insulin at bed time plus pre meals inhaled insulin (recent)

Adjustment:

Increase **or** decrease insulin dose by 10% to keep:

- Fasting blood glucose = 60-80 mg/dl.
- Post prandial blood glucose below 180 - 220 mg/dl.

NB Ketonemia without dehydration & with normal pH will require 1 or 2 injections of insulin intramuscular or subcutaneous 0.1- 0.2U/kg 1 hour apart to halt ketogenesis.

2. Instructions

* Diet → 3 main meals with 2 snacks.
* In infections increase rapid acting insulin by 10%
* Decrease insulin before exercise

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3. Monitor

a. Daily blood glucose at least 4 times;

- Before break fast
- Before lunch
- Before supper
- At bed time.

Initially test blood glucose also between 12AM & 3AM.to exclude nocturnal hypoglycemia

b. Glycosylated hemoglobin (Hb A_{1C}).

* Fraction of hemoglobin to which glucose has been attached.
* Measured as a percent of total hemoglobin.
* Value: Reflect average blood glucose over previous 2-3 months:
  - Normal, non diabetic → < 6%
  - Good control → 6 – 7.9
  - Fair control → 8 – 9.9
  - Poor control → > 10

(Nelson 2008)

Honey moon period

* Due to residual β-cell function → release insulin so About 75% of new diabetics complain recurrent hypoglycaemia which may recur for weeks to months.
* Advice: never stop insulin but reduce the dose to avoid hypoglycaemia.

Somogi phenomenon

* Due to large insulin dose > 2 u/kg/d → Late nocturnal hypoglycemia occur → ↑↑ anti insulin hormones → early morning hyperglycemia.
* Advice: Reduce the evening intermediate insulin by 10%

Dawn phenomenon

* Due to overnight growth hormone secretion → antagonise insulin action → early morning hyperglycamia.
* Advice: increase the evening intermediate insulin by 10%

Polyuria

Definition: Passage of excessive urine output > 2 litres/m^2

Causes

Endocrinal	Renal	Psychogenic
* Diabetes mellitus * Diabetes inspidus	* Hypokalaemia (<2.5 meq/l). * Renal tubular acidosis * Barttar syndrome * Hypercalcemia (> 13 mg/dl). * Chronic renal failure.	* Compulsory water ingestion

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B.Hyperosmolar Hyperglycemic state

- It is a syndrome that occurs predominantly in patients with type 2 diabetes and is characterized by severe hyperglycemia in the absence of significant ketosis.
- The pathophysiology involved is profound dehydration resulting from a sustained hyperglycemic diuresis.
- Clinical findings are weakness, polyuria, polydipsia, lethargy, confusion, convulsions, and coma.
- HHS is characterized by severe hyperglycemia (frequently >1000 mg/dL) and increased serum osmolality (>320 mOsm/kg). There is little or no ketonemia or acidosis present, and most patients have pH >7.3 and serum bicarbonate >20 mEq/L.
- Patients with HHS also frequently develop neurologic symptoms (focal signs, lethargy, blurry vision, and obtundation) due to severe hyperglycemia and elevated serum osmolality.
- Management of HHS involves high-volume fluid and electrolyte replacement, and insulin.
- Severe hyperglycemia induces an osmotic diuresis, which can lead to a deficit of 8-10 liters in total body water. Fluid replacement with normal saline is the most important initial step in management of hyperosmolar hyperglycemic state.
- Despite normal or elevated serum potassium levels, patients with hyperosmolar hyperglycemic state (HHS) or diabetic ketoacidosis have a total body potassium deficit due to excessive urinary loss caused by glucosuria-induced osmotic diuresis. Aggressive insulin therapy for HHS can lower serum potassium levels further and cause severe hypokalemia.

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
Patient characteristics	• Type 1 diabetes usually • Younger age	• Type 2 diabetes usually • Older age
Clinical symptoms	• Less pronounced altered mentation • More rapid onset of hyperglycemic symptoms • Hyperventilation & abdominal pain common	• More pronounced altered mentation • Gradual onset of hyperglycemic symptoms • Hyperventilation & abdominal pain less common
Laboratory studies	• Glucose 250-500 mg/dL (13.9-27.8 mmol/L) • Bicarbonate <18 mEq/L (18 mmol/L) • Elevated anion gap • Positive serum ketones • Serum osmolality <320 mOsm/kg (320 mmol/kg)	• Glucose >600 mg/dL (33.3 mmol/L) • Bicarbonate >18 mEq/L (18 mmol/L) • Normal anion gap • Negative or small serum ketones • Serum osmolality >320 mOsm/kg (320 mmol/kg)

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

Sun

Seconed:Chronic complications:

- Chronic complications of diabetes involve the macro- and microvasculature, and are a major result of disease progression.
- Microvascular disease of diabetes includes diabetic nephropathy, neuropathy, and retinopathy.
- Macrovascular disease contains coronary artery disease, peripheral arterial disease, and stroke.
- Optimization of glycemic control in diabetes mellitus is associated with a reduced risk of microvascular complications (nephropathy, retinopathy). However, the benefits in preventing macrovascular complications (myocardial infarction, stroke, peripheral arterial disease) have not been firmly established.

A.Macrovascular Disease

- The number 1 cause of death in patients with diabetes is cardiovascular disease. About 75% of all deaths in diabetes are from myocardial infarction, congestive failure, or stroke.
- The central pathological mechanism in macrovascular disease is atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system.
- Lipid testing should be performed in patients with diabetes at least annually. Diabetes is considered the equivalent of coronary disease in terms of management of hyperlipidemia. Lipid goals for adults with diabetes are: LDL <100 mg/dL (or <70 mg/dL in cases of overt CVD).
- Diabetic patients age 40-75 should receive statin therapy regardless of baseline lipid levels.

B.Microvascular Disease:

B1.Diabetic Nephropathy:

- Diabetes is the most common cause of end-stage renal disease in the United States.
- Diabetic nephropathy begins with hyperfiltration (increased glomerular filtration rate - GFR) and microalbuminuria (levels of albumin between 30 and 300 mg per 24 hours).
- If not treated adequately, microalbuminuria may progress to macroproteinuria, defined as urine protein excretion >300 mg/24 hr. This increase in urinary protein is accompanied by a progressive decline in GFR.
- Patients with DM should be screened annually for microalbuminuria and started on an ACE inhibitor or ARB when it is present.
- Intensive blood pressure (BP) control is the primary intervention proven to slow the decline in GFR once azotemia develops. Most patients with diabetes mellitus should be treated toward a target BP of 140/90 mm Hg, and patients with diabetic nephropathy may benefit from more intensive BP control. Most guidelines now recommend a target BP of 130/80 mm Hg for patients who are diabetic with signs of nephropathy.
- Angiotensin-converting enzyme (ACE) inhibitors, and perhaps angiotensin receptor blockers (ARBs), are the preferred antihypertensive drugs for patients with diabetes mellitus. These drugs may have actions in addition to BP control, such as reducing intraglomerular pressure, which may be renoprotective. However, ACE inhibitors or ARBs in patients with diabetic nephropathy must be initiated carefully as they may induce an acute decline in GFR and hyperkalemia.
- Several randomized controlled clinical trials have demonstrated the beneficial effects of ACE inhibitors in slowing the progression of diabetic nephropathy. The use of ACE inhibitors reduces urinary albumin excretion and the decline in creatinine clearance. Its use is recommended in patients with microalbuminuria even if their blood pressure is normal, since microalbuminuria is a sensitive marker of renal microvascular damage.

B2.Diabetic Retinopathy:

- DM's effect on microvasculature is especially apparent in the eye. In the United States, nearly 25,000 people go blind from DM each year.

- The only management for non-proliferative retinopathy is tighter control of glucose.

- When neovascularization and vitreous hemorrhages are present, it is called proliferative retinopathy. This is treated with laser photocoagulation, which markedly retards the progression to blindness. VEGF inhibitors treat severe retinopathy.

Vascular endothelial growth factor (VEGF) inhibitors help.

Mon B3. Diabetic Neuropathy:

- Damage to microvasculature damages the vasonervorum that surrounds large peripheral nerves.

- Neuronal injury in diabetes is due to a number of factors, including microvascular injury, demyelination, oxidative stress, and deposition of glycosylation end products. This leads to a length-dependent axonopathy, with clinical features occurring first in the longest nerves (feet).

- Neuropathy is another complication of diabetes, and it has various types:

A. Peripheral neuropathy (most common):

- Diabetes mellitus is the most common cause of peripheral neuropathy, with the risk related to the duration of disease and glycemic status.

- Symmetric distal sensorimotor polyneuropathy is the most common neuropathy in patients with diabetes, and clinical features depend on the type of nerve fibers involved:
  - Small fiber injury is characterized by predominance of positive symptoms (pain, paresthesias, allodynia).
  - Large fiber involvement is characterized by predominance of negative symptoms (numbness, loss of proprioception and vibration sense, diminished ankle reflexes).

- Podiatric exam (microfilament testing) should occur annually to look for early signs of neuropathy since it leads to increased injury from trauma.

- Diabetes is responsible for 50% of all nontraumatic amputations in the United States.

B. Mononeuropathy:

- Affects a single nerve or nerve trunk (mononeuritis multiplex) and is vascular in origin; patients will have sudden foot drop, wrist drop, or paralysis of CN III, IV, or VI.

C. Autonomic neuropathy:

- Can be devastating; patients will have orthostatic hypotension and syncope as main manifestations.

- Autonomic dysregulation can lead to decreased sweating and dry feet (susceptible to skin fissure formation) and further increase the risk for ulceration.

- After several years, DM decreases the ability of the gut to sense the stretch of the walls of the bowel. Stretch is the main stimulant to gastric motility.

- Diabetic gastroparesis (delayed gastric emptying) presents with symptoms of anorexia, nausea, vomiting, early satiety, postprandial fullness, and impaired glycemic control. Hypoglycemic episodes can occur with insulin administration prior to meals in patients with impaired gastric emptying or delayed absorption. Prokinetic agents (metoclopramide, erythromycin, cisapride) are useful in the management of symptoms.

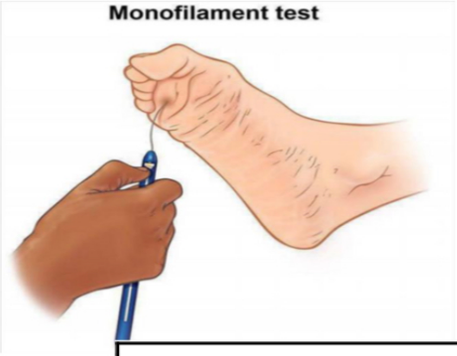
- Bladder dysfunction or paralysis can lead to urinary retention.

- Impotence and retrograde ejaculation can occur; the prevalence of erectile dysfunction is as high as 50% in patients with 10 years of diabetes.

- As with other microvascular complications, prevention of neuropathy in diabetes is by tight glycemic control.

- Initial treatment options for painful diabetic neuropathy include tricyclic antidepressants (amitriptyline), dual serotonin norepinephrine reuptake inhibitors (duloxetine), and anticonvulsants (pregabalin, gabapentin). Pregabalin is a structural analogue of gamma-aminobutyric acid and decreases pain by inhibiting the release of excitatory neurotransmitters by binding to voltage-gated calcium modulators on nerve terminals.

- Erectile dysfunction is treated with sildenafil and similar drugs.
- Neuropathic ulcers most commonly occur in the feet under bony prominences, such as the metatarsal heads. They typically have a punched-out or undermined border.





Diabetic foot ulcers	
Risk factors	• **Diabetic neuropathy** (loss of protective sensation, small muscle atrophy, abnormal vascular tone, decreased sweating with fissures) • **Arterial insufficiency** • End-stage renal disease in a patient on dialysis • Smoking
Location	• Plantar surface, areas under pressure points (eg, bony prominences)
Management	• Mechanical offloading • Debridement • Wound dressings • Antibiotics if infection

- Foot infections are common in patients with diabetes mellitus. Risk is increased in those with poor glycemic control (impaired immunity), neuropathy (impaired recognition), and/or peripheral artery disease (impaired healing). Symptoms usually start with localized skin erythema, warmth, tenderness, and edema.
- Deeper infections should be suspected in those with long-standing wounds (>1- 2 weeks), systemic symptoms (fever, chills), large ulcer size (>2 cm), elevated erythrocyte sedimentation rate, and the presence or palpation of bone in the ulcer base.
- Underlying osteomyelitis is common due to contiguous spread from the wound.
- Patients with any of these features almost always have polymicrobial infections with a mixture of gram-positive (Staphylococcus aureus, Streptococcus pyogenes), gram-negative (Pseudomonas aeruginosa), and anaerobic organisms.

❖ N.B:

- Metabolic syndrome includes hypertension, impaired fasting glucose, and dyslipidemia. Patients are also characteristically overweight, with predominantly central (abdominal) fat distribution that is reflected by an increased waist-to-hip ratio. Insulin resistance plays a central role in the pathogenesis of metabolic syndrome.
- Metabolic syndrome is diagnosed when at least 3 of the 5 following criteria are met:

- Abdominal obesity (Men: Waist circumference >40 inches; Women: Waist circumference >35 inches).
- Fasting glucose >100 -110 mg/dL.
- Blood pressure > 130/80 mm Hg.
- Triglycerides >150 mg/dL.
- HDL cholesterol (Men: <40 mg/dL; Women: <50 mg/dL).

Third:Complications of the treatment

Hypoglycemiam

- occurs most frequently in the **early neonatal period**, often as a result of inadequate energy stores to meet the large metabolic needs of premature or SGA newborns.
- Hypoglycemia in the first few days of life in an otherwise normal newborn is less frequent and warrants concern.
- After 2 to 3 days of life, hypoglycemia is less common and is more frequently the result of endocrine or metabolic disorders.
- **Serum glucose concentrations < 45 mg/dL** (abnormal and necessitate treatment).
- Serum glucose < 55 mg/dL can occur in normal individuals, especially with prolonged fasting→ suspect, if + symptoms of hypoglycemia.
- The **diagnosis** of hypoglycemia should be made on the basis of:
  1. low serum glucose concentration
  2. symptoms compatible with hypoglycemia
  3. resolution of the symptoms after administration of glucose.

A. General principles

1. **Definition.** This is a controversial area, particularly in the neonate. However, at plasma glucose levels <60 mg/dL counter-regulatory responses (cortisol, GH, and glucagon secretion) designed to raise glucose levels are activated.
2. **It is important to recognize hypoglycemia early,** especially in newborns and young infants, when the brain is dependent on glucose for proper neurodevelopment.
3. The **symptoms of hypoglycemia** are age dependent and vary in each patient.
   a. **Newborns or infants** may have varied symptoms that include lethargy, myoclonic jerks, cyanosis, apnea, or seizures.
   b. **Older children** may have symptoms similar to adults, including tachycardia, diaphoresis, tremors, headaches, or seizures.

CLINICAL MANIFESTATIONS

- The symptoms and signs of hypoglycemia result from direct depression of the CNS owing to lack of energy substrate and the counterregulatory response to low glucose via catecholamine secretion.

SYMPTOMS AND SIGNS OF HYPOGLYCEMIA

FEATURES ASSOCIATED WITH EPINEPHRINE RELEASE*	FEATURES ASSOCIATED WITH CEREBRAL GLYCOPENIA
Perspiration	Headache, Hunger
Palpitation (tachycardia)	Mental confusion
Pallor	Inability to concentrate, Somnolence
Paresthesia	Dysarthria
Trembling	Personality changes
Anxiety	Staring, Diplopia
Weakness	Convulsions ,Ataxia
Nausea	Stroke
Vomiting	Coma

- The manifestations in infants differ compared with the manifestations in older children.
- Symptoms and signs of hypoglycemia in infants are nonspecific and include:
  1. jitteriness
  2. feeding difficulties
  3. pallor
  4. hypotonia
  5. hypothermia
  6. episodes of apnea and bradycardia
  7. depressed levels of consciousness
  8. seizures

Jitteriness is an involuntary movement that is particularly frequent in the newborn. Its hallmark is tremor. The pathogenesis is poorly understood.

- In older children, symptoms and signs include:
  1. confusion & irritability
  2. headaches
  3. visual changes
  4. tremors
  5. pallor
  6. sweating
  7. tachycardia
  8. weakness& seizures
  9. coma
- Failure to recognize and treat severe prolonged hypoglycemia can result in serious long-term morbidity, including mental retardation and nonhypoglycemic seizures.

B. **Neonatal hypoglycemia.** This condition may be transient (most common) or persistent (less common). (See also Chapter 4, section XIII.)

1. **Transient neonatal hypoglycemia** is usually detected by screening protocols established for high-risk infants (including prematurity, a history of perinatal asphyxia or fetal distress, sepsis, small for gestational age and large for gestational age infants, and infants of diabetic mothers).
2. **Persistent neonatal hypoglycemia** is defined as hypoglycemia that persists for longer than 3 days. Typically, the diagnosis is based on differentiating ketotic from nonketotic hypoglycemia. Ketones (specifically β-hydroxybutarate) that are detectable at the time of an episode of hypoglycemia indicate ketotic hypoglycemia. The differential diagnosis of persistent neonatal hypoglycemia includes the following:
    a. **Nonketotic hypoglycemia**
        1. **Hyperinsulinism due to perinatal stress, genetic defects leading to islet cell hyperplasia, or Beckwith–Wiedemann syndrome:** Patients with Beckwith–Wiedemann syndrome can be LGA and present with visceromegaly, hemihypertrophy, macroglossia, umbilical hernias, and distinctive ear creases. Treatment for hyperinsulinism may involve diazoxide, octreotide, or surgical resection of the pancreas.
        2. **Fatty acid oxidation defects**
    b. **Ketotic hypoglycemia**
        1. **Hormone deficiencies**, including GH deficiency and cortisol deficiency. **(Key point: Congenital hypopituitarism should be suspected in the neonate who presents with hypoglycemia, microphallus, and midline defects such as a cleft palate.)**
        2. **Hereditary defects in carbohydrate metabolism** (e.g., glycogen storage disease type I and galactosemia) or **amino acid metabolism** (e.g., maple syrup urine disease, methylmalonic acidemia and tyrosinemia) See also Chapter 5, sections VI and VII, and Table 5-5).

C. **Hypoglycemia in infancy and childhood.** Hypoglycemia is relatively uncommon in older infants and children, but the differential diagnosis is extensive and includes the following:

1. **Ketotic hypoglycemia** is the **most common cause of hypoglycemia in children 1–6 years of age.** This form of hypoglycemia typically occurs in the morning in the presence of ketonuria and a low insulin level. This appears to be an **inability to adapt to a fasting state.** Typically these children are thin and become hypoglycemic after intercurrent infection or prolonged fast. Treatment includes avoiding prolonged fasts and giving foods with long-acting carbohydrates at bedtime (i.e., corn starch).

2. **Ingestions** must always be considered in the differential diagnosis of hypoglycemia in the older child, especially in adolescents.
    a. **Alcohol** metabolism in the liver can deplete essential cofactors needed for adequate gluconeogenesis, resulting in hypoglycemia (especially when the child is in the fasting state).
    b. **Oral hypoglycemic agents**
3. **Inborn errors of metabolism**
4. **Hyperinsulinism,** as described in section XII.B.2.a

Sun

Classification of Hypoglycemia in Infants and Children

Abnormalities in the Hormonal Signal Indicating Hypoglycemia
Counterregulatory Hormone Deficiency
Panhypopituitarism
Isolated growth hormone deficiency
ACTH deficiency
Addison disease
Glucagon deficiency
Epinephrine deficiency
Hyperinsulinism
Infant of a diabetic mother
Infant with erythroblastosis fetalis
Persistent hyperinsulinemic hypoglycemias of infancy
Beta cell adenoma (insulinoma)
Beckwith-Wiedemann syndrome
Anti-insulin receptor antibodies
Inadequate Substrate
Prematurity/small for gestational age infant
Ketotic hypoglycemia
Maple syrup urine disease
Disorders of Metabolic Response Pathways
Glycogenolysis
Glucose-6-phosphatase deficiency
Amylo-1,6-glucosidase deficiency
Liver phosphorylase deficiency
Glycogen synthase deficiency
Gluconeogenesis
Fructose-1,6-diphosphatase deficiency
Pyruvate carboxylase deficiency
Phosphenolpyruvate carboxykinase deficiency
Fatty Acid Oxidation
Long, medium, or short chain fatty acid acyl-CoA dehydrogenase deficiency
Carnitine deficiency (primary or secondary)
Carnitine palmitoyltransferase deficiency
Other
Enzymatic defects
Galactosemia
Hereditary fructose intolerance
Propionicacidemia
Methylmalonic acidemia
Tyrosinosis
Glutaric aciduria
Global hepatic dysfunction
Reye syndrome
Hepatitis
Heart failure
Sepsis, shock
Carcinoma/sarcoma (IGF-2 secretion)
Malnutrition-starvation
Hyperviscosity syndrome
Drugs/Intoxications
Oral hypoglycemic agents, Propranolol, Pentamidine, Quinine , Trimethoprim-sulfamethoxazole (with renal failure), Insulin,Alcohol, Salicylates, Valproic acid, Ackee fruit (unripe)

Important Notes:

- There are two important causes of hypoglycemia in non-diabetic patients with elevated insulin level:

1. Insulinoma (beta cell tumor).
2. Surreptitious use of insulin or sulfonylurea.

- Helpful tests used in the evaluation of hypoglycemic patients are measurements of c-peptides, proinsulin and sulfonylurea levels. Elevated C-peptide levels and proinsulin levels greater than 5 pmol/L are seen in patients with beta cell tumors.

Differential Diagnosis of Insulinoma and Factitious Hyperinsulinism

Test	Insulinoma	Exogenous Insulin	Sulfonylureas
Plasma insulin	High (usually <200 µU/mL)	Very high (usually >1,000 µU/mL)	High
Proinsulin	Increased	Normal or low	Normal
C peptide (insulin connective peptide) 1:1	Increased	Normal or low	Increased
Insulin antibodies	Absent	+/– Present	Absent
Plasma or urine sulfonylurea	Absent	Absent	Present

- When the plasma glucose concentration is low, there is an increase in the body's secretion of epinephrine, glucagon, and, to a lesser extent, cortisol and growth hormone.

- The increase in sympathetic activity stimulates lipolysis in the peripheral tissues and gluconeogenesis in the liver and decreases peripheral glucose consumption. The brain relies heavily on glucose as an energy source, and the level of glucose uptake by the brain is not regulated by insulin. If hypoglycemia persists despite this autonomic reaction, the activity of higher brain centers diminishes in order to reduce glucose requirements. Thus, there are two types of hypoglycemic symptoms:

- Adrenergic symptoms such as sweating, tremor, palpitations, hunger, and nervousness occur due to epinephrine and norepinephrine release. Adrenergic symptoms are the early signs of hypoglycemia.
- CNS symptoms develop later and at lower glucose levels. They include behavioral changes, confusion, visual disturbances, stupor, and seizures. Prolonged CNS hypoglycemia leads to irreversible neurological deficits and death.

- Non-selective B-blockers (propranolol, timolol and nadolol) inhibit the epinephrine and norepinephrine-mediated compensatory reactions to hypoglycemia. Thus, the adrenergic symptoms of hypoglycemia (tremor, palpitations) are blunted. Additionally, blockade of B_2 adrenergic receptors inhibits hepatic gluconeogenesis and peripheral glycogenolysis and lipolysis.

- Non-selective B-blockers exacerbate hypoglycemia and mask its adrenergic symptoms. For this reason, they should not be used in patients with diabetes mellitus. Selective B antagonists should be used instead if a B-blocker is necessary.

- Treatment:

- Blood glucose can be raised to normal within minutes by taking 10-20 grams of carbohydrates; it can be taken as food or drink if the person is conscious and able to swallow.

- If the patient is unconscious or has seizures, we can establish IV access and give intravenous dextrose.

- If IV access cannot be established, the patient can be given intramuscular glucagon injection.

Management of DM. TypeI:

Insulin replacement therapy [30]

- **Treatment options**
  - Multiple daily insulin injections (see "Full basal-bolus insulin regimen" for details)
  - Insulin pump (consider for most patients)
- **Starting dose calculation** [30]
  - Exogenous insulin requirements will depend on the residual insulin production of the pancreas.
  - **Total daily dose** (TDD) of insulin is usually ~ 0.4–1.0 units/kg per day, divided into 50% basal and 50% prandial insulin.
  - Consider initiating treatment with 0.5 units/kg per day.
- **Dose titration**
  - After beginning insulin treatment, there is often a temporary reduction in exogenous insulin demand. [43]
  - Dosage should be adjusted according to glycemic monitoring.

> Educate patients on calculating insulin requirements throughout the day and in accordance with activities and meals. [30]

Other treatment strategies [30]

- **Noninsulin antidiabetics**: not generally used in T1DM treatment
- **Pancreas and islet transplantation**
  - Can improve glucose control but are not standard treatments because of the need for lifelong immunosuppressive therapy
  - May be considered in patients:
    - With recurrent episodes of diabetic ketoacidosis or severe hypoglycemia despite adequate treatment
    - Undergoing simultaneous renal transplantation or patients with a previous renal transplant

Thu

Inusulin

Insulin Regimens

Many types of insulin differ in duration of action and time to peak effect (Table 171.2). These insulins can be used in various combinations, depending on the needs and goals of the individual patient. The most commonly used regimen is that of multiple injections of fast-acting insulin given with meals in combination with long-acting basal insulin given at bedtime. This regimen provides flexibility but requires administration of many injections per day and will require assistance for young children. After the total daily dose of insulin is determined, 30-50% is given as long-acting insulin, and the remainder is given as fast-acting insulin, divided according to the need for corrections of high glucose levels and for meals. To correct for hyperglycemia, one can determine the insulin sensitivity using the 1,800/1,500 rule: dividing 1,800 (or 1,500) by the total daily dose of insulin to determine how many milligrams per deciliter of glucose will decrease with one unit of insulin. The insulin:carbohydrate ratio is used to calculate insulin for the carbohydrate content of food; 500 divided by the total daily dose determines the number of grams of carbohydrate that requires one unit of insulin.

Insulin pumps that provide a continuous SC infusion of short-acting insulin also are available and are being used by children and adolescents who are highly motivated to achieve tight control.

Lispro, aspart, and glulisine insulin are synthetic human insulin analogs in which amino acid alterations result in fast absorption and onset of action (see Table 171.2). Because of the short duration of action, these are used in combination with long-acting insulin. Glargine and detemir are insulin analogs with increased solubility at acidic pH and decreased solubility at physiological pH. They have a duration of greater than 24 hours and act as a basal insulin.

Newly diagnosed patients in the honeymoon period may require 0.4-0.6 U/kg/24 hr. Prepubertal patients with diabetes longer than 1-2 years typically require 0.5-1 U/kg/24 hr. During middle adolescence when elevated GH concentrations produce relative insulin resistance, insulin requirements increase by 40-50%, and doses of 1-2 U/kg/24 hr are typical.

TABLE 171.2 Representative Profiles of Insulin

INSULIN	ONSET	PEAK ACTION	DURATION
VERY SHORT ACTING			
Lispro, aspart, glulisine	5-15 min	30-90 min	3-5 hr
SHORT ACTING			
Regular	30-60 min	2-3 hr	5-8 hr
INTERMEDIATE ACTING			
Neutral protamine Hagedorn (NPH) (isophane)	2-4 hr	4-10 hr	10-16 hr
LONG ACTING			
Glargine	2-4 hr	None	20-24 hr
Detemir	2-4 hr	6-14 hr	16-20 hr
Degludec	2-4 hr	None	24+ hr

Data from Wolfsdorf JI, ed. Intensive Diabetes Management. *4th ed. Alexandria, VA: American Diabetes Associations; 2009.*

Blood Glucose Testing

Blood glucose should be routinely monitored before each meal and at bedtime. Hypoglycemia during the night or excessive variability in the morning glucose concentrations should prompt additional testing at 2 or 3 A.M. to ensure that there is no consistent hypoglycemia or hyperglycemia. During periods of illness or when blood glucose concentrations are higher than 300 mg/dL, urine ketones also should be tested. Continuous glucose monitors, which provide minute-to-minute blood glucose concentration information, can be useful in following trends of blood glucose concentrations, but should not be used in calculations of mealtime insulin doses.

Long-Term Glycemic Control

Measurements of **glycohemoglobin** or **hemoglobin A_{1c} (HgbA1c)** reflect the average blood glucose concentration over the preceding 3 months and provide a means for assessing long-term glycemic control. HgbA1c should be measured four times a year, and the results should be used for counseling of patients. The American Diabetes Association has set HgbA1c targets for children at <7.5%. Measurements of HgbA1c are inaccurate in patients with hemoglobinopathies. Glycosylated albumin or fructosamine can be used in these cases.

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TypeII DM:

Pathophysiology

T2D can occur as the result of various pathophysiological processes; however, the most common form results from peripheral insulin resistance and compensatory hyperinsulinemia, followed by failure of the pancreas to maintain adequate insulin secretion (see Table 171.1).

Epidemiology

The prevalence of T2D in children is increasing in parallel with childhood obesity and is highest in children of ethnic groups with a high prevalence of T2D in adults, including Native Americans, Hispanic Americans, and African Americans. Obesity, the metabolic syndrome, ethnicity, and a family history of T2D are risk factors. Autoantibodies to the pancreas are present among some clinically assumed to have T2D, compounding the difficulty in differentiating T1D from T2D at the time of diagnosis.

Clinical Manifestations and Differential Diagnosis

Fasting and postprandial glucose levels for diagnosis of T2D are the same as those for T1D. The diagnosis of T2D may be suspected on the basis of polyuria and polydipsia in a background of the metabolic syndrome. Differentiating T2D from T1D in children on only clinical grounds can be challenging. The possibility of T2D should be considered in patients who are obese, have a strong family history of T2D, have other characteristics of the metabolic syndrome, or have absence of antibodies to β cell antigens at the time of diagnosis of diabetes. **Acanthosis nigricans,** a dermatological manifestation of hyperinsulinism and insulin resistance, presents as hyperkeratotic pigmentation in the nape of the neck and in flexural areas and is noted as a sign in the metabolic syndrome. Although ketoacidosis occurs far more commonly in T1D, it also can occur in patients with T2D under conditions of physiological stress and cannot be used as an absolute differentiating factor. T2D can be confirmed by the evaluation of insulin or C-peptide responses to stimulation with oral carbohydrate and in the absence of islet cell autoreactivity.

Therapy

T2D is the result of a combination of insulin resistance, relative insulin deficiency, and a secretory β cell defect. Asymptomatic patients with mildly elevated glucose values (slightly >126 mg/dL for fasting or slightly >200 mg/dL for random glucose) may be managed initially with lifestyle modifications, including nutrition therapy (dietary adjustments) and increased exercise. Exercise has been shown to decrease insulin resistance. In most children with new-onset, uncomplicated T2D, oral agents are usually the first line of therapy. Only metformin, an insulin secretagogue, is approved by the U.S. Food and Drug Administration for use in children. A rare side effect of metformin is lactic acidosis, occurring mainly in patients with compromised renal function. The most common side effect is gastrointestinal upset. If ketonuria or ketoacidosis occurs, insulin treatment is necessary to first achieve adequate glycemic control, but may be discontinued within weeks with continuation of oral medications. Insulin therapy may be required if adequate glycemic control is not achieved with lifestyle modifications and metformin.

Because T2D may have a long preclinical course, early diagnosis is possible in subjects at risk who have the **metabolic syndrome.** Significant lifestyle modifications, such as improved eating habits and increased exercise, have a role in preventing or decreasing the morbidity of T2D. Finally, it is critical to monitor and manage the other components of metabolic syndrome, such as advanced pubertal development, hypertension, hyperlipidemia, and polycystic ovary syndrome in females.

Approach [30]

- Start treatment in all patients at diagnosis. [30][44]
  - Monotherapy with **metformin** is the first-line initial treatment for most patients.
  - If there are contraindications for metformin, choose a different noninsulin antidiabetic, depending on patient factors.
- Consider early combination pharmacological therapy in select patients, e.g., those with: [31][30]
  - Clinical ASCVD, high ASCVD risk, heart failure, or CKD
  - HbA1c ≥ 1.5% above the glycemic target
  - Indications for insulin therapy for T2DM at time of diagnosis
- Reevaluate treatment and treatment adherence every 3–6 months. [30]
  - Sequentially add noninsulin antidiabetic drugs until glucose targets are met.
  - If targets are still not met despite adequate treatment:
    - Add an injectable GLP-1 receptor agonist.
    - Consider insulin therapy.

Metformin should be part of every patient's treatment, unless contraindicated, and continued for as long as it is tolerated, as it is safe, effective, widely available, and has been shown to reduce cardiovascular events and mortality. [30]

Noninsulin antidiabetics

Noninsulin antidiabetics for the treatment of type 2 diabetes mellitus [30]

Drug class	Examples	Important considerations
Biguanides	• **Metformin** DOSAGE	• Drug of choice, unless there are contraindications for metformin
Dipeptidyl peptidase-4 inhibitor	• Sitagliptin DOSAGE • Saxagliptin DOSAGE • Linagliptin DOSAGE	• Avoid saxagliptin in patients with heart failure.
SGLT-2 inhibitors	• Empagliflozin DOSAGE	• Recommended for patients with CKD and confirmed eGFR 15-29 mL/min/1.73 m2 • Consider in patients with clinical ASCVD or high risk of ASCVD, chronic kidney disease, or congestive heart failure. • Beneficial for patients who need to lose or maintain their weight
GLP-1 receptor agonists	• Semaglutide ◦ Oral DOSAGE ◦ Injectable DOSAGE • Other subcutaneous GLP-1 receptor agonists ◦ Daily liraglutide DOSAGE ◦ Weekly dulaglutide DOSAGE	• Recommended for patients with eGFR < 30 mL/min/1.73 m2 • Consider in patients with clinical ASCVD, high risk of ASCVD. • Beneficial for patients who need to lose or maintain their weight
Sulfonylureas	• Glimepiride DOSAGE	• Increases risk for hypoglycemia • Low cost
Thiazolidinedione	• Pioglitazone DOSAGE	• Avoid in patients with congestive heart failure. • Low cost

Indications for insulin therapy in T2DM [30]

- Patients whose glycemic targets are not met despite sufficient antidiabetic treatment
- Patients with contraindications for noninsulin antidiabetic drugs, e.g., patients with end-stage renal failure
- Pregestational and gestational diabetes [46]
- Hyperglycemic crisis
- Consider in newly diagnosed patients with any of the following:
  - Initial glucose ≥ 300 mg/dL or HbA1c > 10%
  - Symptoms of hyperglycemia
  - Signs of a continued catabolic state, e.g., weight loss

Approach to insulin treatment in T2DM [30]

- Start with the simplest insulin regime, i.e., a basal insulin regimen with once-daily injections.
- Titrate the insulin dose according to individualized glycemic targets and tolerance.
- Consider adding prandial insulin or switching to a mixed insulin regimen as needed.
- Noninsulin antidiabetics may be continued when insulin treatment is started.
- See "Insulin regimens" for details.

GLP-1 receptor agonists should be part of the treatment strategy prior to starting insulin treatment in patients with T2DM, unless they are not appropriate or insulin therapy is preferred.

If treatment goals are not met in a patient on a basal insulin regimen, combination therapy with basal insulin and injectable GLP-1 receptor agonists may be considered.

Overview of antidiabetic drugs

Class	Agents	Mechanism of action	Side effects	Contraindications	Interactions
Insulinotropic					
Sulfonylureas	• First generation ◦ Chlorpropamide ◦ Tolbutamide • Second generation ◦ Glyburide ◦ Glimepiride ◦ Glipizide	• Increase insulin secretion from pancreatic β cells	• **Risk of hypoglycemia** (second generation) • **Weight gain** • Disulfiram-like reaction (first generation) • Hematological changes: agranulocytosis, hemolysis	• Severe cardiovascular comorbidity • Obesity • Severe renal or liver failure • Sulfonamide allergy (particularly long-acting substances)	• Biguanides: Concomitant use may be associated with an increase in cardiovascular mortality.
Meglitinides	• Nate**glin**ide • Repa**glin**ide		• **Risk of hypoglycemia** • **Weight gain**	• Severe liver failure	• Sulfonylureas: ↑ risk of hypoglycemia
Dipeptidyl peptidase-4 (DPP-4) inhibitors	• Saxa**glip**tin • Sita**glip**tin • Linagliptin	• Inhibit GLP-1 degradation → ↑ glucose-dependent insulin secretion	• **Gastrointestinal symptoms** • **Pancreatitis** • Nasopharyngitis, upper respiratory tract infection • Headache, dizziness • Arthralgia • Edema	• Liver failure • Moderate to severe renal failure	• CYP3A4/5 inhibitors: ↑ concentration of saxagliptin [1]
Glucagon-like peptide-1 (GLP-1) agonists (incretin mimetic drugs)	• Exenatide • Liraglutide • Albiglutide • Semaglutide	• Stimulate the GLP-1 receptor directly	• ↑ Risk of **pancreatitis** and possibly pancreatic cancer • Nausea	• Preexisting, symptomatic gastrointestinal motility disorders	• Warfarin: ↑ INR [2]

Noninsulinotropic					
Biguanides	• Metformin	• Enhances the **effect** of insulin	• **Lactic acidosis** (possible triggers: dehydration, infection, renal impairment) • Weight loss • Gastrointestinal complaints are common (e.g., diarrhea, abdominal cramps) • ↓ Vitamin B12 absorption	• **Chronic kidney disease** • Metformin **must be paused** before administration of iodinated contrast medium and major surgery.	• Sulfonylureas: Concomitant use may be associated with an increase in cardiovascular mortality.
Sodium-glucose cotransporter 2 (SGLT-2) inhibitors	• Cana**glif**lozin • Dapa**glif**lozin • Empa**glif**lozin	• Increase glucose excretion with urine through the inhibition of SGLT-2 in the kidney	• **Genital yeast infections** and UTIs • Glucosuria • Polyuria and dehydration • Diabetic ketoacidosis • Weight loss • Potentially carcinogenic effects are being investigated (breast cancer, bladder cancer)	• Recurrent urinary tract infections • Chronic kidney disease	• No severe drug interactions [3]
Alpha-glucosidase inhibitors	• Acarbose	• Decrease intestinal glucose absorption	• **Gastrointestinal symptoms** (flatulence, diarrhea, feeling of satiety)	• Severe renal failure • Any preexisting intestinal conditions (e.g., inflammatory bowel disease)	• Other antidiabetics: hypoglycemia [4]
Thiazolidinediones	• Pio**glit**azone • Rosi**glit**azone	• Reduce insulin resistance through the stimulation of peroxisome proliferator-activated receptors (PPARs) • Increase transcription of adipokines	• **Edema** • **Cardiac failure** • **Weight gain** • ↑ Risk of bone fractures (osteoporosis) • ↑ LDL	• Congestive heart failure • Liver failure	• CYP2C8 inhibitors (e.g., gemfibrozil): ↑ concentration of glitazones [5]
Amylin analogs	• **Pramlintide**	• Decrease glucagon release • Slow gastric emptying • Increase feeling of satiety	• Risk of hypoglycemia • Nausea	• Gastroparesis	• Delayed effect of concomitantly administered drugs due slowed gastric emptying (e.g, ampicillin, acetaminophen) [6]

Mody DM

MATURITY-ONSET DIABETES OF YOUTH (MODY)

MODY comprises a group of dominantly inherited forms of relatively mild diabetes. Insulin resistance does not occur in these patients; instead, the primary abnormality is an insufficient insulin secretory response to glycemic stimulation. Treatment depends on the type and can include the use of sulfonylureas.

- **MODY** (maturity-onset diabetes of the young): genetic defects leading to β-cell dysfunction
  - Different forms of autosomal dominant inherited diabetes mellitus that manifest before the age of 25 years and are not associated with obesity or autoantibodies
  - Multiple monogenic subtypes (most common: MODY II due to glucokinase gene defect, and MODY III, due to **hepatocyte nuclear factor**-1-α gene defect)
  - MODY II
    - A single mutation leads to impaired insulin secretion due to altered glucokinase function.
    - Glucokinase is the glucose sensor of the β cell, facilitating storage of glucose in the liver, especially at high concentrations.
    - There is no increased risk of microvascular disease.
    - Despite stable hyperglycemia and chronically elevated HbA_{1C} levels, MODY II can be managed with diet alone.
  - All other subtypes, including MODY III, require medical treatment either with insulin or sulfonylureas.

Thu

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