Chapter 118 – Diabetes Mellitus and Disorders of Glucose Homeostasis

Episode Overview

- There are four ways to diagnose diabetes, through random plasma glucose, fasting plasma glucose, a 75g glucose tolerance test, and through the hemoglobin A1c. In the emergency department, the most relevant test is the random glucose as patients may present this way.
- DKA is diagnosed by the presence "D" for diabetes - hyperglycemia, "K" for ketosis, or a presence of serum or urine ketones, and "A" for acidosis, an anion gap acidosis.
- The essential treatment of DKA includes restoration of intravascular volume, insulin to halt ketosis and to correct acidosis, correction of electrolyte disturbances such as potassium/magnesium levels. Don't forget to treat the underlying cause!
- Use of sodium bicarbonate to correct acidosis in DKA has not demonstrated any benefit and may be associated with worse outcomes.
- A hyperglycemic hyperosmolar state is usually seen in older adults with multiple comorbid conditions and is distinguished from DKA by the absence of ketoacidosis. In addition to fluid resuscitation and correction of hyperglycemia, treatment should address the underlying cause of the state, which includes infection, myocardial infarction, and cerebrovascular accident. (Think of those 6 I's)
- Diabetic peripheral neuropathy is common and has multiple treatment modalities, including gabapentin, pregabalin, and duloxetine.
- Diabetic foot ulcers and other diabetic soft tissue infections (e.g., gas gangrene, Fournier's gangrene) are frequently polymicrobial and require broad-spectrum antibiotic therapy covering gram-positives, gram-negatives, and anaerobes.
- Hypoglycemia may be associated with significant morbidity and mortality. When the diagnosis is suggested and, if possible, confirmed by laboratory evaluation, therapy should be initiated immediately.
- Hypoglycemia caused by sulfonylurea oral hypoglycemic agents may be prolonged. Patients should be observed for an extended period or hospitalized.

Core Questions

1. Define DKA.
2. List 6 potential triggers of DKA.
3. Describe the pathophysiology of DKA.
4. How is DKA managed in children and in adults?
5. What are the epidemiologic risk factors for cerebral edema in DKA?
6. What are signs and symptoms of cerebral edema? How do you manage a patient with DKA and suspected cerebral edema?
7. List 5 complications of DKA management.
8. List 5 common serious infections in diabetics and how they are managed.
9. How does hypoglycemia classically present?
10. List 10 causes of hypoglycemia
11. Describe the treatment of hypoglycemia
12. What is the definition of hyperglycemic, hyperosmolar state?
13. Contrast DKA and HHS.
14. What is the pathophysiology of HHS?
15. How is HHS managed?

Wisecracks

1. Why are urine ketones less sensitive for DKA than serum ketones?
2. When do you give sodium bicarbonate to a patient with DKA?
3. What is euglycemic DKA?
4. What is the differential diagnosis of hypoglycemia in a patient who does not have DM? What would you add to the differential diagnosis in a patient who has DM?

Rosen's In Perspective:

This is an important topic - the complications of diabetes lead to immense morbidity and mortality. Our body (specifically the brain) needs a tight control on serum glucose for optimal functioning - this podcast is all about what happens when the balance is off.

- Normally, our body's glucose is derived from three sources—intestinal absorption from the diet, endogenous production from the breakdown of glycogen (glycogenolysis), and the formation of glucose from precursors (gluconeogenesis), including lactate, pyruvate, amino acids, and glycerol.

- Insulin receptors on the beta cells of the pancreas sense elevations in the blood glucose concentration and trigger insulin release into the blood. It sticks around for 3-10 minutes before it is broken down in the liver and kidney.

- Our body maintains glucose homeostasis through endogenous glucose production and dietary glucose intake. There are many complex hormonal regulatory pathways to achieve this. Glucose regulatory hormones include insulin, glucagon, epinephrine, cortisol, and growth hormone.

- Insulin is the main glucose-lowering hormone.

- The American Diabetes Association (ADA) defines four major types of diabetes mellitus:

  - Type 1 Diabetes Mellitus = autoimmune-related
    - Typically seen in lean patients under the age of 40 (usually has onset at 10 years-old)

  - Type 2 Diabetes Mellitus = typically lifestyle-related
    - Most often seen in middle-aged or older patients who are overweight (80%), with normal to high insulin levels

  - Gestational Diabetes

  - Diabetes due to a Secondary Process
    - Patients with chronic pancreatitis, cystic fibrosis, genetic defects in beta cells or insulin receptors, post-surgical patients (e.g., Whipple's procedure), and chemical-induced (e.g., Vacor, chemotherapeutic agents, antipsychotics, antiretroviral medications, and glucocorticoids)

- The 1997 National Diabetes Data Group reported discontinued use of the terms "insulin dependent diabetes mellitus" and "non–insulin-dependent diabetes mellitus" because they were confusing and clinically inaccurate. In addition, the use of Arabic numerals, 1 and 2, instead of Roman numerals is the standard. Impaired glucose tolerance (IGT) has been replaced by the term prediabetes to identify individuals at high risk for the development of diabetes. The pathogenesis of prediabetes is thought to be related to insulin resistance.

NOTE: Type 1 diabetes results from a chronic autoimmune process that usually exists in a preclinical state for years. The classic manifestations of type 1—hyperglycemia and ketosis—occur late in the course of the disease, and are an overt sign of beta cell destruction.

Core Questions

[1] Define diabetic ketoacidosis (DKA)

DKA is a syndrome in which insulin deficiency and glucagon excess combine to produce a hyperglycemic, dehydrated, acidotic patient, with profound electrolyte imbalance.

Let's emphasize the key points here:
- Insulin deficiency
- Hyperglycemia
- Dehydration and electrolyte imbalance
- Anion-gap metabolic acidosis

[2] List 6 potential triggers for DKA

DKA most commonly occurs in patients with type 1 diabetes and is associated with inadequate administration of insulin, infection, or myocardial infarction. DKA can also occur in type 2 diabetics and may be associated with any type of stress, such as sepsis or GI bleeding. Approximately 25% of all episodes of DKA occur in patients whose diabetes was previously undiagnosed.

Typical Triggers:
- Non-adherence to insulin
- Equipment error / medication miscalculation
- Infection (of any type)
  - Pneumonia
  - Cholecystitis
  - Pyelonephritis
- Myocardial infarction
- GI bleeding
- Emotional stress

NOTE: Remember the 6 I's - Infection, Infarction, Intoxication, Intraabdominal process, Initial diagnosis, Insulin misuse (both forgetfulness as well as non-adherence)

[3] Describe the pathophysiology of DKA

Please refer to Figure 118.1 from Rosen's Emergency Medicine: Concepts and Clinical Practice, 9th Edition for a diagrammatic explanation of diabetic ketoacidosis.

Here is a stepwise version:
1. Trigger: cessation of insulin intake or by physical or emotional stress, despite continued insulin therapy.
2. When the hyperglycemia becomes sufficiently marked, the renal threshold is surpassed, and glucose is excreted in the urine.
   a. The hyperosmolarity produced by hyperglycemia and dehydration is the most important determinant of the patient's mental status.
3. Glucose in the renal tubules draws water, sodium, potassium, magnesium, calcium, phosphorus, and other ions from the circulation into the urine.
   a. This osmotic diuresis, combined with poor intake and vomiting, produces the profound dehydration and electrolyte imbalance associated with DKA
4. Insulin deficiency results in activation of a hormone-sensitive lipase that increases circulating free fatty acid (FFA) levels.
   a. Long-chain FFAs, now circulating in abundance as a result of insulin deficiency, are partially oxidized and converted in the liver to acetoacetate and β - hydroxybutyrate.
   b. Despite the increased pathologic production of ketones, the body acts as it does in any form of starvation to decrease the peripheral tissue's use of ketones as fuel.
5. The combination of increased ketone production with decreased ketone use leads to ketoacidosis.
   a. Acidosis plays a prominent role in the clinical presentation of DKA.
6. The acidotic patient attempts to increase lung ventilation to rid the body of excess acid with Kussmaul's breathing. Bicarbonate is used up in the process. Acidosis compounds the effects of ketosis and hyperosmolality to depress mental status directly.
   a. Acidemia is not invariably present, even with significant ketoacidosis.
   b. Ketoalkalosis has been reported in diabetic patients vomiting for several days and in some with severe dehydration and hyperventilation.

[4] How is DKA managed in children and adults?

NOTE:

For managing DKA in pediatric populations, refer to the BCCH DKA protocols here: http://www.bcchildrens.ca/health-professionals/clinical-resources/endocrinology-diabetes/dka-protocol

Also refer to the DKA Medical protocol from BC Children's Hospital here: http://www.bcchildrens.ca/endocrinology-diabetes-site/documents/dkaprtfill.pdf

Here's a breakdown for pediatrics:
- Resuscitate → repair electrolytes/fluids → replace insulin → reassess and confirm DKA: plasma glucose (PG) ≥11 mmol/L, ketones, capillary pH ≤7.3, HCO3– ≤15 mmol/L

Resuscitate:
- Calculate body weight, and administer a normal saline fluid bolus to correct any shock state/orthostatic hypotension (5-20 ml/kg over 1-2 hrs)

Repair:
- Calculate maintenance fluid requirements and administer NS - use the worksheet or estimate using 4-2-1- rule
- ******Wait 1-2 hrs before starting IV insulin*****
    - Insulin given in the first 1–2 h of DKA repair is thought to increase mortality. This insulin rate fully inhibits ketogenesis and gluconeogenesis and should be maintained if possible.

Replace:
- Calculate and start a piggyback insulin drip at 0.05–0.1 units/kg BW/h:
    - No insulin boluses
- When you start insulin, you should be adding potassium to the IV fluids! (could add it to the maintenance fluid)
- Replace lost electrolytes

Reassess:
- Add dextrose to keep serum glucose between 10-15 mmol/L
- Keep [K+] >4.0 mmol/L; Correct Mg.
- Notes:
    - Bicarbonate is not generally recommended
    - Q1 hr glucose checks
    - Q2-3 hrs electrolyes and creatinine checks.
    - Watch for cerebral edema

Here's a breakdown for adults:
- Remember, we're typically looking for the triad of:
    - Hyperglycemia, acidosis, and ketosis
- However, various states can knock one of these things out of the triad (e.g. severe vomiting producing a hypercholoremic state with little acidosis due hyperventilation and HCl loss causing metabolic alkalosis).
- With adults, we're more aggressive with replacing K+ and insulin. Check out the box in Rosen's.
- Follow this outline:
    1. ABC's (for the rare case that needs intubation - be concerned!)
    2. If hypotensive or orthostatic - bolus fluids
    3. Start IV fluids
    4. Start insulin (if [K+] is > 3.5 mmol/L)
        a. Consider SC insulin if mild DKA: e.g. they aren't altered, don't have N/V/D
        b. Use IV:
            i. Regular insulin infused at 0.1 units/kg/hr up to 5 to 10 units/hr, mixed with IV fluids.
            ii. Bolus not usually needed
    5. Continue IV fluids and add in:
        a. KCl when [K+] is < 4.5mmol/L
        b. Dextrose when glucose falls below 15 mmol/L
        c. Correct Mg

[5] What are the epidemiologic risk factors for cerebral edema in DKA?

Despite frequently voiced concerns about this complication, it remains rare, with an overall incidence of 1% in pediatric DKA patients. Virtually all current evidence supporting the contention that the use of higher doses of insulin and aggressive fluid resuscitation contribute to the development of cerebral edema has come from retrospective reviews and small case studies. The best available evidence shows associations only with lower $PaCo_2$ and higher blood urea nitrogen levels, indicating that severity of disease, rather than treatment interventions, plays the most significant role.

Rosen's List of associating risk factors in DKA for cerebral edema:
- Low $PaCO_2$ - hyperventilation
- Higher BUN - very dehydrated
- Age < 5 years - very fragile, tight brain

The BC guidelines footnote - in children:
- Subclinical brain swelling is common in children with DKA. Cerebral edema (CE) accounts for more than half of the 1−5% mortality rate of DKA in children.
- ****At highest risk are***
    - Newly diagnosed patients
    - Those aged <5 years
    - Those with initial pH <7.1 or pCO2 <18.
    - Aggressive hydration has been implicated in several studies
    - Bicarbonate infusions/boluses have been implicated as well

[6] What are the signs and symptoms of cerebral edema? How do you manage a patient with DKA and suspected cerebral edema?

Signs and symptoms of cerebral edema include:
- Altered level of consciousness
- Coma

NOTE: These signs and symptoms are occurring despite the correction of acidosis. Cerebral edema generally occurs 6 to 10 hours after the initiation of therapy; there are no warning signs, and the associated mortality rate is 90%.

In children:
Close neurological observation and frequent rousing of the child with finger-pokes to detect any changes consistent with cerebral edema are indicated. Follow Glasgow Coma Scale. Severe headache, change in sensorium or BP, dilated pupils, bradycardia, irregular breathing, posturing and incontinence are signs of impending deterioration.

Rapid intervention is imperative:
- Airway / breathing / circulation
- Elevate head of bed
- Decrease fluid rate by one-third
- Mannitol (0.5–1 g/kg IV over 20 min) or 3% NaCl (5–10 mL/kg IV over 30 min)

- Consider intubation and mild hyperventilation (keep $PaCO_2$ >22 mg Hg) for impending respiratory failure
- Arrange CT when stable

[7] List 5 complications of DKA management

Morbidity in DKA is largely iatrogenic:
- Hypokalemia from inadequate potassium replacement due to shift by the IV insulin
- Hypoglycemia from inadequate glucose monitoring
- Failure to replenish glucose in IV solutions when the serum glucose concentration drops below ~13-15 mmol/L
- Alkalosis from overaggressive bicarbonate replacement
- Pulmonary edema from over aggressive hydration
- Hypophosphatemia (produces severe multi-organ dysfunction and altered LOC)
- Cerebral edema (usually presents 6-10 hrs after initiating therapy!)

NOTE: The mortality rate in treated DKA is approximately 5-7%. The primary causes of death remain infection, especially pneumonia, arterial thromboses, and shock.

NOTE: Cerebral edema remains an important cause of morbidity and mortality in children with DKA (unlikely when age > 5 years).

[8] List 5 common serious infections in diabetics and how they are managed?

Diabetic patients are more susceptible to complications of infections because of their inability to limit microbial invasion with effective polymorphonuclear leukocytes and lymphocytes**.**

Infections include:
- Pyelonephritis
- Tuberculosis
- Mucocutaneous candidiasis
- Intertrigo
- Mucormycosis
- Soft tissue infections
- Non-clostridial gas gangrene
- Osteomyelitis
- Malignant pseudomonas otitis externa

Refer to Table 118.3 from Rosen's Emergency Medicine: Concepts and Clinical Practice, 9th Edition for a complete table outlining the antimicrobial therapies for serious infections in diabetics. A summarized table is provided below.

Infectious Condition	Antimicrobial Therapy
Diabetic Foot Infection	Mild • Consider TMP-SMX, 800/160 BID or Clindamycin 300 mg q6h Moderate to Severe • Clindamycin 600 mg IV q6h +/- Piptazo 3.375 g IV q6h and Vancomycin 15 mg/kg IV q12h
Malignant Otitis Externa	Oral • Ciprofloxacin 500 mg PO BID for 10-14 days IV • Ceftazidime 2 g IV q8h +/- Gentamicin 2 mg/kg IV q8h
Mucormycosis	Amphoteracin B 1-1.5 mg/kg/day OR Posaconazole 400 mg BID
Mucocutaneous Candidiasis	Ketoconazole 200 mg PO daily; may need several weeks of therapy
Non-clostridial Gas Gangrene (including Fournier's)	Clindamycin 600 mg q6h + third-generation cephlasporin + Vancomycin 15 mg/kg q12h

NOTE: Occult osteomyelitis should be considered in all cases of neuropathic ulceration

[9] How does hypoglycemia classically present?

The Brain needs glucose. The CNS cannot synthesize glucose, store more than a few minutes' supply, or concentrate glucose from the circulation. Prolonged severe hypoglycemia may cause cellular death. To protect against hypoglycemia, the body brings about cessation of insulin release and mobilization of counterregulatory hormones, which increase hepatic glucose production and decreases glucose use. Diabetic patients using insulin are particularly vulnerable to hypoglycemia because of insulin excess and failure of the counterregulatory system (even one episode of hypoglycemia can permanently impair the neurohormonal systems and lead to hypoglycemia without awareness) - autonomic neuropathy, and decreased epinephrine secretion or sensitivity.

Symptoms of hypoglycemia:
- Depends upon the rate at which the glucose level decreases, however, and the patient's age, gender, size, overall health, and previous hypoglycemic reactions contribute to symptom development.
- For example:
  - In patients with hypoglycemia unawareness, the prodrome to marked hypoglycemia may be minimal or absent, and these individuals may rapidly become unarousable. They may have a seizure or show focal neurologic signs, which resolve with glucose administration.
- For most other patients: signs and symptoms of hypoglycemia are caused by excessive secretion of epinephrine and CNS dysfunction; these include
  - Sweating
  - Nervousness/Tremor
  - Tachycardia
  - Hunger
  - Neurologic symptoms, ranging from bizarre behavior and confusion to seizures and coma.

[10] List 10 causes of hypoglycemia

Causes of hypoglycemia in the non-diabetic can be thought about in terms of decreased production of glucose, increased usage of glucose, and increased insulin or other hypoglycemic compounds:

- Decreased Production - inadequate glucose production includes hormone deficiencies, enzyme defects, substrate deficiencies, severe liver disease which causes poor stores

Causes of overuse of glucose include the presence of:

- Exogenous insulin and sulfonylureas (from someone with diabetes), other drugs, endotoxic shock, insulinoma, extrapancreatic tumors, and a variety of enzyme deficiencies that can cause congenital hyperinsulinism

Causes of hypoglycemia in the diabetic:

- Consider their own medications, such as with excess insulin or other oral hypoglycemic agents

Use the "DIMES" approach (coupled with how UpToDate does it):

- **Drugs:**
  - o Insulin
- **Insulin secretagogues:**
  - o Alcohol
  - o Others - e.g. indomethacin, quinine
- **Infection / illnesses:**
  - o Sepsis
- **Metabolic:**
  - o Liver, renal failure
  - o Adrenal insufficiency
  - o Type 1 diabetic - without glucagon
- **Environmental:**
  - o Accidental, surreptitious, or malicious hypoglycemia
- **Structural:**
  - o Insulinomas

[11] Describe the treatment of hypoglycemia

In alert patients with mild symptoms:
- Oral consumption of sugar-containing foods or beverages

In comatose/altered patients:
- One to three ampules of D50W is administered IV while the patient's airway, breathing, and circulation are assessed and maintained.
- Add Thiamine if the patient is an alcoholic
- Start a dextrose infusion ASAP (because blood sugars often drop again!)

- If IV access cannot be rapidly obtained, 1 to 2 mg of glucagon may be given intramuscularly or subcutaneously.

  - The onset of action is 10 to 20 minutes, and a peak response occurs in 30 to 60 minutes. It may be repeated as needed. Glucagon may also be administered IV; 1 mg has an effect similar to that of one ampule of D50W. Glucagon is ineffective in causes of hypoglycemia in which glycogen is absent, notably alcohol-induced hypoglycemia.

Note: PO Hypoglycemics
- Treatment of hypoglycemia secondary to oral hypoglycemic agents depends on the agent. Metformin and the thiazolidinediones rarely cause significant or prolonged hypoglycemia, whereas sulfonylureas, which are insulin secretagogues, do cause hypoglycemia. Sulfonylurea oral hypoglycemic agents pose special problems because the hypoglycemia they induce tends to be prolonged and severe. Patients with an overdose of sulfonylurea hypoglycemic agents should be observed for a period of 24-hours if hypoglycemia recurs in the ED after management of the initial episode.
- A patient with hypoglycemia from sulfonylureas, in addition to standard glucose replacement, frequently requires treatment with an agent to inhibit further insulin release, such as octreotide, a somatostatin analogue.
  - Adult doses have ranged from 50 to 100 µg IV or subcutaneously every 12 hours
  - Pediatric dosages of 0.1 mcg/kg IV or subcutaneously.

[12] What is the definition of hyperglycemic, hyperosmolar state?

Definition: A syndrome of acute diabetic decompensation characterized by marked hyperglycemia, hyperosmolarity, dehydration, and decreased mental function that may progress to frank coma.

Let's highlight these again:
- Acute diabetic decompensation
- Hyperglycemia
- Hyperosmolarity
- Dehydration
- Altered mental status

NOTE: Ketoacidosis is generally minimal or absent, although metabolic acidosis from another source, such as lactic acidosis from sepsis or uremia from acute renal failure, may be present. Focal neurologic signs may be present, or there may be a global encephalopathy.

NOTE: DKA and HHS may occur together.

[13] Contrast DKA and HHS

Refer to Table 118.2 from Rosen's Emergency Medicine: Concepts and Clinical Practice, 9th Edition for a complete table contrasting DKA and HHS

Disease State	DKA	HHS
Glucose	High	VERY high
Serum sodium	Normal-low ~130 mmol/L	Normal-high ~140 mmol/L
Potassium	Spectrum - can be low or high Falsely normal in acidosis	Usually normal
Bicarbonate	Usually < 10 mmol/L	Usually > 15 mmol/L
Serum ketones	PRESENT	ABSENT
Electrolyte Anomalies	Potassium, magnesium, and phosphorus deficits are usually marked - masked by severe acidosis and dehydration	Highly elevated serum osmolarity, and elevated BUN
Age	Young	Elderly

[14] What is the pathophysiology of HHS?

HHS is most common in geriatric patients with type 2 diabetes, but has been reported in children with type 1 diabetes. HHS may occur in patients who are not diabetic, especially after burns, parenteral hyperalimentation, peritoneal dialysis, or hemodialysis. Often, the patient is prevented from taking in adequate fluids because of stroke, Alzheimer's disease, or other diseases, greatly exacerbating the dehydration.

Causes of HHS:
- Any condition that produces hyperglycemic diuresis

Here are the key points:
- Usually an elderly patient with renal dysfunction harbors the environment to produce the disease:
    - Decreased insulin action results in glycogenolysis, gluconeogenesis, and decreased peripheral uptake of glucose.
        - Hyperglycemia pulls fluid from the intracellular to the extracellular space
- This fluid is lost in a profound osmotic diuresis, limited finally by hypotension and a subsequent drop in the glomerular filtration rate (GFR)
- Hypotonic diuresis produces profound dehydration, leading to hyperglycemia, hypernatremia, and associated hypertonicity

Why the absence of ketoacidosis (unless they have a concurrent starvation ketosis) in HHS?
- Unknown. FFA levels are lower than in DKA, thus limiting the substrates needed to form ketones. The most likely reason for the blunted counterregulatory hormone release and lack of ketosis seems to be the continued secretion of tiny amounts of insulin that block ketogenesis.

[15] How is HHS managed?

Here are the key points:
Our treatment for HHS is similar to that of DKA, however usually these patients have cardiac disease, pulmonary disease and renal disease - they can't usually tolerate overly aggressive resuscitation to well.

- Isotonic IV fluids (bolus in cases of hypotension) - to correct the dehydrated state
- Careful assessment, monitoring and replacement of electrolytes
- SC insulin is usually adequate to control sugars; consider IV insulin infusion for very high levels (>35 mmol/L)
- Assess for and treat the underlying cause
- Phenytoin is contraindicated in hyperosmolar hyperglycemic non-ketotic coma (HHNC) because of its impairment of endogenous insulin release and ability to precipitate HHNC.
- DVT prophylaxis

Wisecracks

[1] Why are urine ketones less sensitive for DKA than serum ketones?

Answer: Urine ketone dipsticks use the nitroprusside reaction, which is a good test for acetoacetate but does not measure β-hydroxybutyrate. Although the usual ratio of acetoacetate to β-hydroxybutyrate in DKA is 1:2.8, it may be as high as 1:30, in which case the urine dipstick does not reflect the true level of ketosis. When ketones are predominantly in the form of β-hydroxybutyrate, the urine ketone dipstick may infrequently yield negative reactions even in patients with significant ketosis.

[2] When do you give bicarbonate to a patient with DKA?

Answer: Unless needed to stave off impending cardiac arrest in a severely acidemic patient, we do not recommend routine bicarbonate administration.

[3] What is euglycemic DKA?

Answer: Euglycemic DKA (blood glucose level ≤ 16.6 (300 mg/dL))

This phenomenon has been reported in up to 18% of patients. Categories of oral agents may be divided into those that increase the insulin supply, including sulfonylureas, secretagogues, and insulin itself. Medications that decrease insulin resistance include the biguanides and thiazolidinediones; drugs that reduce the rate of glucose absorption include α-glucosidase inhibitors. The specific drugs we are worried about are: Sodium-Glucose Cotransporter 2 Inhibitors. Dapagliflozin (Forxiga), canagliflozin (Invokana), and empagliflozin (jardiance), and SGLT2 are sodium-glucose cotransporter 2 inhibitors. SGLT2 is a protein that transports filtered glucose from the proximal renal tubule into tubular epithelial cells, enhancing urinary excretion levels of glucose.

[4] What is the differential diagnosis of hypoglycemia in a patient who does not have DM? What would you add to the differential diagnosis in a patient who has DM?

Answer:

Causes of hypoglycemia in the diabetic:
- Excess insulin (overdose)
- Decreased dietary intake of fuels
- Increase demands

Causes of hypoglycemia in the non-diabetic:
- Inadequate glucose production includes hormone deficiencies, enzyme defects, substrate deficiencies
- Severe liver disease
- Drugs - alcohol, indomethacin, quinine, oral hypoglycemics

Causes of overuse of glucose include the presence of:
- An insulinoma, exogenous insulin, sulfonylureas, drugs, endotoxic shock, extrapancreatic tumors, and a variety of enzyme deficiencies.

Clinical Pearl: The most common reason for a patient to have a low glucose is too much insulin or exposure to oral hypoglycemic agents. However, in patients without diabetes who are presenting with hypoglycemia, it is important to rule out alcoholism, severe sepsis, adrenal insufficiency, and panhypopituitarism. Insulinoma is rare and should be a diagnosis of exclusion. Always consider surreptitious use if no obvious cause found, especially if there is possibility of access to diabetic drugs.