DIABETIC KETOACIDOSIS

DKA
INTRODUCTION:- Definitions, and terms

Diabetic ketoacidosis (DKA) is an emergency medical condition, and a dangerous complication of diabetes mellitus in which the chemical balance of the body becomes far too acidic.

If not treated properly, the metabolic acidosis from the accumulation of ketones can be life-threatening.

Diabetic ketoacidosis (DKA) always results from severely depressed insulin levels.

Insulin is the hormone secreted by the body to lower the blood sugar levels when they become too high.
Diabetes mellitus is the disease resulting from the inability of the body to produce or respond properly to insulin, required by the body to convert glucose to energy.

DKA is a metabolic acidosis from the accumulation of ketones due to severely depressed insulin levels.

Diabetic ketoacidosis is a potentially fatal complication of diabetes that occurs when blood-glucose levels are high (often above 400 mg/dL).

Diabetic ketoacidosis (DKA) results from grossly deficient insulin availability, causing a transition from glucose to lipid oxidation and metabolism.
• **WHO GETS IT**
  
  Diabetic ketoacidosis occurs most often in patients with type 1 diabetes (formerly called insulin-dependent diabetes mellitus) under 19 years of age. It is usually caused by the **interruption of their insulin treatment** or by **acute infection or trauma**.
  
  People with type 1 diabetes are at risk of diabetic ketoacidosis. **It rarely occurs in people with type 2 diabetes.** In about **25 percent** of children with diabetes, symptoms from ketoacidosis are the first sign that they have diabetes.
  
  In type I DM patients, DKA is commonly precipitated by a lapse in insulin treatment or by an acute infection, trauma, or infarction that makes usual insulin treatment inadequate.
  
  Recent studies suggest that it **can sometimes be the presenting condition in obese black patients with newly diagnosed type 2 diabetes** (formerly called non-insulin-dependent diabetes mellitus).
• A small number of people with type II diabetes also experience ketoacidosis, but this is rare given the fact that type II diabetics still produce some insulin naturally.

• When DKA occurs in type II patients, it is usually caused by a decrease in food intake and an increased insulin deficiency due to hyperglycemia. People with type 2 diabetes usually develop ketoacidosis only under conditions of severe stress. Poor compliance with diet and treatment is usually the cause when episodes are recurrent.

• Diabetic ketoacidosis can occur because a diabetic has stopped taking normal insulin injections or is not taking enough insulin. It also can be triggered by an infection or severe physical stress, such as an injury or surgery.
• Although type II DM patients rarely have DKA, many may have ketone formation and acidosis (usually mild) because of a decrease in food intake and a marked decrease in insulin secretion due to severe and chronic hyperglycemia (glucose toxicity). These patients usually do not require insulin after the acute metabolic event is corrected.

• **REMEMBER**: Diabetic ketoacidosis may lead to the initial diagnosis of type 1 diabetes, as it is often the first symptom that causes the person to come to medical attention.

• **REMEMBER MOST ILLNESSES MAKE DIABETES WORSE & DIABETES MAKE MOST ILLNESSES WORSE**

• This is why **infection, trauma, heart attack, or surgery can lead to diabetic ketoacidosis in type 1 diabetics especially.**
• **Precipitating Factors For the Development of DKA:**

• When considering the precipitating factors for the development of DKA it is important to remember that DKA develops due to either an absolute or a relative absence of insulin.

• An absolute insulin deficiency is the major precipitant for those patients presenting in DKA who have new onset type I diabetes. It is estimated that 10-20% of patients with new onset diabetes will present in DKA as their initial presentation.

• Another major cause of absolute insulin deficiency is omission of normal insulin in a patient with known type I diabetes.

• In those patients with known diabetes the precipitating factor for DKA can be identified in greater than 80% of the cases. So take a proper history if possible OR GET IT FROM THE RELATIVES
• Except in the case where the patient stops taking their insulin, the usual cause of the DKA is a relative lack of insulin. Relative insulin deficiency occurs when there is an increased requirement for insulin due to an increased physiologic stress such as seen with an infection, trauma, or other process.

• **Infection** is the most frequent identifiable cause of DKA with pneumonia and urinary tract infections being two of the most common causes.

• **Myocardial infarction** should always be considered in the list of precipitating factors of DKA, particularly in older patients, as the condition is associated with elevations of epinephrine which may stimulate a pathologic process that results in DKA.
• Other precipitating causes are noted in the table below.

**Precipitating Factors of DKA:**

• **Relative lack of Insulin:**

• **Acute Illness**
  • * Infection or other inflammatory process
  • * Myocardial Infarction
  • * Stroke
  • * Trauma

• **Endocrine Disorders**

• **Drugs:**
  • * Steroids * Calcium channel blockers
  • * Pentamidine * Beta-blocking agents
  • * Dilantin * Alcohol
  • * HCTZ
• **INCIDENCE**

• The incidence of this condition may be increasing, and a 1 to 2 percent mortality rate has stubbornly persisted since the 1970s.
WHAT IS REALLY HAPPENING IN DKA PHYSIOLOGICALLY – THE PATHOGENESIS & PATHOPHYSIOLOGY

To understand what happens in DKA, it is helpful to understand the normal process of glucose metabolism.

After absorption of food glucose concentrations in the blood increase and then slowly fall over a period of several hours. Under normal circumstances the body is able to maintain blood glucose within a narrow range during both the feeding and fasting states due to a complex interplay between insulin and a catabolic hormone called glucagon.
In the period between meals there is a relative insulin lack, which allows a mobilization of free fatty acids from adipose tissue. When this occurs, metabolism shifts slightly so that the lipids are used by peripheral tissues for energy rather than glucose. This allows the remaining glucose to be available to tissues such as the brain.

It is important to be aware that brain cells are both insulin insensitive (they do not require insulin for transport of glucose into the cells) and primarily use glucose for energy.

This means that the brain continues to use glucose as its fuel, even during fuel deprivation, starvation, and DKA.
• When insulin levels decrease in DKA, large quantities of fatty acids are released from the fat cell, into the blood.

• These free fatty acids are taken up by the liver where, in the setting of decreased insulin and increased glucagon, become the precursors for ketoacid production.

• In addition, the elevated free fatty acid levels increase gluconeogenesis within the liver, increasing the glucose levels even more.

• If there were no free fatty acids there would be no DKA.
• Some of the fatty acids released are taken up by the liver and converted to ketones which can be oxidized in the brain to provide backup fuel should hepatic glucose production fail.

• These changes are typical of the post-prandial phase and would usually end at the next meal.

• **If the fasting period is extended the ketone levels will begin to rise**, but usually are limited by the fact that ketones stimulate insulin release which prevents further breakdown of adipose tissue.

• Obviously, in severe starvation conditions this mechanism can be overridden so that adipose stores can be used.
• DKA can be viewed as a state of absolute or relative insulin deficit and increased levels of counter-regulatory hormones (glucagon, catecholamines, cortisol, growth hormone).

• As discussed above, under normal conditions these hormones balance out their actions on the fat cells and the liver allowing for well regulated management of glucose and lipids within the liver and adipose tissues. BUT........

• In cases where the counter-regulatory hormones outweigh the effects of insulin, for whatever reason, DKA supervenes.
In some ways, DKA can be seen as starvation in the midst of plenty.

Clearly, there is an excess of glucose, the normal substrate used for energy production.

Unfortunately, without the presence of insulin, the glucose goes largely unused since most cells are unable to transport glucose into the cell without the presence of insulin.

Many of the cells in the body feel as though they are starving and they innocently activate homeostatic mechanisms to provide even greater quantities of glucose, thus resulting in greater hyperglycemia.

In response to the sense of starvation, other alternative fuels, such as ketoacids and fatty acids, are produced.

Despite these fuels, the majority of cells remain "hungry" and continue to order more food production.
• And so……more and MORE GLUCOSE is produced!!!

• The manner in which this "food" production is undertaken in this pathological situation is discussed below.
• Pathological Changes Within the Liver:

• In the setting of insulin deprivation three organs are primarily affected, the liver, the fat cell, and the muscle.

• Many of the pathological changes seen in DKA are less the result of an absolute lack of insulin, as they are the result of an alteration in the balance of insulin and the other counter-regulatory enzymes.
When the balance is working appropriately, insulin normally works to promote synthetic and storage pathways in the following ways:

- (1) stimulates hepatic glycogenesis,
- (2) stimulates pyruvate production which is used in the synthesis of amino acids, lipids, and ATP production,
- (3) simulates lipogenesis.

Glucagon does exactly the opposite of insulin and when glucagon is present in excess it multiplies the problems that were initiated by the lack of insulin.

For example, glucagon stimulates the breakdown of glycogen into glucose, increases glucose formation from pyruvate and inhibits lipogenesis.
The inhibition of lipogenesis allows a cascade of other reactions to occur which has the end result of increasing the flow of free fatty acids into the liver mitochondria where they are oxidized into the ketoacids (acetoacetate and beta-hydroxybutyrate).
• **Changes in Other Organs:**

• While all these actions are occurring within the fat cells and the liver, other detrimental changes are also occurring.

• When the serum glucose level rises above 300 mg/dl it exceeds the ability of the kidney to reabsorb it and glucose begins to appear in the urine.

• Glucose is an osmotically active molecule and when it is present in the urine it pulls with it water and electrolytes.

• The ketoacids are also released into the urine as non reabsorbable anions of sodium and potassium salts which adds to the loss of electrolytes.

• The increased glucose levels affect the serum in a manner similar to that seen in the kidneys. **The glucose is restricted to the extracellular space and acts to pull water from the intracellular space to the extracellular space. Initially, this fluid shift helps maintain the extracellular volume that is being lost in the urine.**
• However, as the osmotic diuresis continues, **severe intracellular and extracellular dehydration result.**

• Those **patients with normal kidney function, and an ability to remain well hydrated, can excrete large amounts of glucose within the urine without becoming markedly dehydrated. Their glucose levels in DKA may be only moderately elevated.**

• Those patients with severe vomiting, inability to take in adequate urine eventually become markedly dehydrated which results in decreased glomerular filtration rates and a considerably **increased serum glucose level.**
Potassium deserves special attention in the patient with DKA. As a rule, the total body potassium levels in the patient with DKA are decreased.

However, the patient may be hyperkalemic or have a normal serum potassium level at presentation. This falsely normal or elevated plasma potassium level is multifactorial.

First, the osmotic pull of the extracellular fluid shifts water and potassium out of the intracellular fluid of the muscle cells. The shift is then further increased by the breakdown of intracellular protein which liberates more potassium. Additionally, potassium moves out of cells in exchange for hydrogen ions which are present in excess during DKA.

Finally, in the absence of insulin potassium is unable to move back into cells once it has been pulled out. All of this potassium that is pulled from the intracellular arena is initially brought to the kidneys, where it is lost in the osmotic pull present due to the extreme glucosurea.

When the patient finally becomes so dehydrated that they cannot maintain adequate glomerular filtration, the potassium present in the extracellular fluid appears as a normal or increased amount, despite severe total body depletion.
• Diabetic ketoacidosis is a triad of hyperglycemia, ketonemia and acidemia, each of which may be caused by other conditions.
• DKA combines three major features:
• hyperglycemia, meaning excessively high blood sugar levels;
• hyperketonemia, meaning an overproduction of ketones by the body; and
• acidosis, meaning that the blood has become too acidic.
• Insulin deficiency is responsible for all three conditions.
• The diagnostic criteria for DKA include
  • a glucose greater than 250 mg/dl,
  • a pH lower than 7.30-7.35,
  • a low HCO3,
  • an elevated anion gap, and
  • positive serum ketones greater than 1:2 dilution with the nitroprusside reaction
• People with diabetes lack sufficient effective insulin, the hormone needed to allow the body to use glucose (a simple sugar) for energy

• Insulin helps glucose to pass from the bloodstream into body cells, where it is burned as an energy source, and it prevents excessive release of stored glucose by the liver. It normally is produced by the pancreas, but people with type 1 diabetes (insulin-dependent diabetes) don't produce an adequate quantity of insulin, and must inject it daily to control their blood glucose.
But in DKA insulin levels are very low, and the body glucose goes largely unused since most cells are unable to transport glucose into the cell without the presence of insulin; 

this condition makes the body use stored fat as an alternative source instead of the unavailable glucose for energy, a process that produces acidic ketones, which build up because they require insulin to be broken down.

The presence of excess ketones in the bloodstream in turn causes the blood to become more acidic than the body tissues, which creates a toxic condition.
• Lets say this again, another way. In DKA, insulin levels are very low.

• When insulin levels are too low, glucose levels in the blood rise (HYPERGLYCEMIA) and body cells go hungry. Without access to glucose, body cells are forced to burn fat for energy.

• When glucose is not available, body fat is broken down instead. There is therefore an INCREASED LIPOLYSIS.

• The by-products of this increased fat metabolism are acidic chemicals called ketone bodies that are toxic at high concentrations.

• These ketone bodies accumulate in the blood, seriously altering the normal chemistry of the blood and interfering with the function of multiple organs.

• The build up of ketone bodies in the blood, causes the blood to becomes more acidic than body tissues, causing an ACIDEMIA and KETOACIDOSIS.

• The urine also becomes too acid. ACIDURIA.

• The result of the ACIDEMIA (i.e the blood becoming abnormally acidic), is vomiting and abdominal pain.
• If the blood becomes more acidic, \textit{ketoacidosis} can cause falling blood pressure, coma and death.

• The ketone bodies are

• 1- acetone

• 2-acetoacetate

• 3- hydroxybutyric acid
Blood glucose levels become elevated (usually higher than 300 mg/dL)

HYPERGLYCEMIA

a) because of accelerated gluconeogenesis in the liver to produce glucose to try to combat the problem

b) because cells cannot take up that glucose without insulin and there is decreased glucose utilization.

c) because as water is lost from the body, the blood (including the glucose that it contains) becomes more concentrated.

d) because of the reductions in effective concentrations of circulating insulin

e) because of the concomitant elevations of counterregulatory hormones (catecholamines, glucagon, growth hormone and cortisol).

f) because continued urinary losses leads to progressive dehydration and volume depletion, which causes diminished urine flow and greater retention of glucose in plasma. The net result of all these alterations is hyperglycemia

g) because the osmotic diuresis in this condition results in a concentration of the plasma contents

h) because the elevated free fatty acid levels increase gluconeogenesis within the liver, increasing the glucose levels even more
Ketoacidosis is always accompanied by **DEHYDRATION**, which is caused by high levels of blood glucose.

- When blood sugar levels are very high some sugar "overflows" into the urine (**GLYCOSURIA**).
- When sugar is carried away in the urine, water, **salt and potassium are drawn into the urine with each sugar molecule**, and the body loses large quantities of fluid because the volume of urine produced is much larger than normal.
- Usually in DKA, the patient can't drink enough fluids to keep up with the pace of urine production. They urinate frequently, despite increasing dehydration.

- This helps to explain the **POLYURIA AND POLYDIPSIA** in diabetes.
- As water is lost from the body, the blood (including the glucose that it contains) becomes more concentrated.
- Vomiting caused by the blood's acidity also contributes to fluid losses and dehydration. **THERE IS ELECTROLYTE INBALANCE as a result.**
• In DKA, the marked hyperglycemia causes osmotic diuresis; excessive urinary losses of water, Na, and K; and volume contraction with acidosis resulting from increases in hepatic ketone body synthesis and release.

• Hyperglycemia initially causes the movement of water out of cells, with subsequent intracellular dehydration, extracellular fluid expansion and hyponatremia. It also leads to a diuresis in which water losses exceed sodium chloride losses. Urinary losses then lead to progressive dehydration and volume depletion, which causes diminished urine flow and greater retention of glucose in plasma.

• The net result of all these alterations is hyperglycemia with metabolic acidosis and an increased plasma anion gap.
The major ketone bodies, acetoacetic acid and -hydroxybutyric acid obligate additional losses of Na and K. Acetone derived from the spontaneous decarboxylation of acetoacetic acid accumulates in plasma and is slowly disposed of by respiration; it is a CNS anesthetic, but the cause of coma in DKA is unknown.

The abnormal ketogenesis in DKA results from the loss of insulin's normal modulating effect on free fatty acid (FFA) released from adipose tissue and on hepatic FFA oxidation and ketogenesis. Plasma FFA levels and FFA uptake by the liver are greatly increased.

In the liver, insulin normally regulates FFA oxidation and ketogenesis by indirectly inhibiting the transport of coenzyme A derivatives of long chain FFA across the inner mitochondrial membrane into the mitochondrial matrix. Glucagon stimulates hepatic long chain fatty acid-CoA transport and oxidation and ketogenesis in mitochondria, and in DKA the normal opposing effect of insulin is lost.
• Major components of the pathogenesis of diabetic ketoacidosis are

• 1- reductions in effective concentrations of circulating insulin and

• 2-concomitant elevations of counterregulatory hormones (catecholamines, glucagon, growth hormone and cortisol).

• These hormonal alterations bring about three major metabolic events:

• (1) hyperglycemia resulting from accelerated gluconeogenesis and decreased glucose utilization,

• (2) increased proteolysis and decreased protein synthesis and

• (3) increased lipolysis and ketone production.
• Hyperglycemia initially causes the movement of water out of cells, with subsequent intracellular dehydration, extracellular fluid expansion and hyponatremia.

• It also leads to a diuresis in which water losses exceed sodium chloride losses. Urinary losses then lead to progressive dehydration and volume depletion, which causes diminished urine flow and greater retention of glucose in plasma. The net result of all these alterations is hyperglycemia with metabolic acidosis and an increased plasma anion gap.

• The diagnostic criteria for DKA include a glucose greater than 250 mg/dl, a pH lower than 7.30-7.35, a low HCO3, an elevated anion gap, and positive serum ketones greater than 1:2 dilution with the nitroprusside reaction.
• DKA IS ASSOCIATED WITH
• 1- very low insulin levels or deficient insulin availability - there is a reduction in effective concentrations of circulating insulin
• 2- increased glucagon levels
• 3- hyperglycemia -- meaning excessively high blood sugar levels, with metabolic acidosis and an increased plasma anion gap
• 4- increased lipolysis (lipid oxidation)
• 5- increased ketone body formation.
• There is hyperketonemia, meaning an overproduction of ketones by the body
6- academia and aciduria
7- acidosis, meaning that the blood has become too acidic. Note that the acidosis is a metabolic acidosis.
8- vomiting and abdominal pain due to blood becoming abnormally acidic
9- falling blood pressure, coma and death, if the blood becomes very very acidic
10- dehydration—there is a movement of water out of cells, with subsequent intracellular dehydration and extracellular fluid expansion
11- polyuria and polydipsia
12- glycosuria
13- electrolyte imbalances due to excessive urinary losses of water, Na, and K; and volume contraction —there is a hyponatremia
14 osmotic diuresis in which water losses exceed sodium chloride losses—urinary losses then lead to progressive dehydration and volume depletion, which causes diminished urine flow and greater retention of glucose in plasma.
15 abnormal ketogenesis due to the loss of insulin's normal modulating effect on free fatty acid (FFA) released from adipose tissue and on hepatic FFA oxidation and ketosis
• 16- Increased plasma FFA levels and increased FFA uptake by the liver
• 17- elevations of counterregulatory hormones (catecholamines, glucagon, growth hormone and cortisol
• 18- hyperglycemia resulting from accelerated gluconeogenesis and decreased glucose utilization
• 19- increased proteolysis and decreased protein synthesis
• 20- increased lipolysis and ketone production.
• 21 – an increased plasma anion gap
NORMAL CELL

Glucose → Pyruvate → Oxaloacetate → Acetyl-CoA → Ketone bodies

Amino acids

Fatty acids → HS-CoA

Krebs Cycle → Respiratory chain → Energy
Diabetic ketoacidosis

Insulin lack

Increased gluconeogenesis
  - Hyperglycemia
    - Glycosuria
  - Osmotic diuresis
    - Dehydration

Increased lipolysis
  - Increased ketogenesis
    - Hyperketonemia
      - ketonuria
      - Acidosis
        - Hyperventilation
MANAGEMENT OF DKA

• PREVENTATIVE MEASURES
  • Preventive measures include patient education and instructions for the patient to contact the physician early during an illness.
  • If this fails and the patient presents there is need for evaluation of patients with diabetic ketoacidosis.
• An educational program should include sick-day management instructions (i.e., for any illness that alters routine care), including the use of short-acting insulin, blood glucose and urinary ketone monitoring, and the use of a liquid diet containing carbohydrates and salt.

• Patients should not discontinue insulin therapy when they are ill, and they should contact their physician early in the course of illness.

• Indications for hospitalization include greater than 5 percent loss of body weight, respiration rate of greater than 35 per minute, intractable elevation of blood glucose concentrations, change in mental status, uncontrolled fever and unresolved nausea and vomiting.
HISTORY & EXAMINATION

The management of patients with diabetic ketoacidosis includes obtaining a thorough but rapid history and performing a physical examination in an attempt to elucidate possible precipitating factors.

The history and physical examination continue to be important aspects of management. Even in comatose patients, information documenting a history of diabetes or insulin therapy may be available.

The physical examination can provide supportive evidence for the diagnosis of diabetic ketoacidosis and can point to precipitating factors.
• Although usually straightforward, the diagnosis of diabetic ketoacidosis is occasionally missed in unusual situations, such as when it is the initial presentation of diabetes in infants or elderly patients or when patients present with sepsis or infarction of the brain, bowel or myocardium.

• These presentations can distract the physician from the underlying diagnosis of diabetic ketoacidosis.

• The laboratory tests needed to confirm the presence of diabetic ketoacidosis and to screen for precipitating events are summarized in another handout. The essential data can be obtained promptly in the emergency department.
• HOW TO TREAT IT
• IMPORTANT POINTS TO NOTE
• The major goals of treatment are (1) rapid fluid volume expansion in order to improve circulatory volume and tissue perfusion,
• (2) correction of hyperglycemia by administering low-dose insulin and hyperketonemia by clearing ketones from serum and urine at a steady rate,
• (3) prevention of hypokalemia during treatment, and
• (4) identification of and treatment for any associated bacterial infection.
• Rapid correction of the pH by bicarbonate administration is not required in most patients (those with a plasma pH > 7), and such treatment carries significant risks of inducing alkalosis and hypokalemia.

• Close physician supervision is required during treatment for DKA, since frequent clinical and laboratory assessments and appropriate adjustments in treatment are necessary.

• The mortality rate is about 10%; hypotension or coma on admission adversely affects the prognosis.

• The major causes of death are circulatory collapse, hypokalemia, and infection.
• The therapeutic goals for diabetic ketoacidosis consist of
  • improving circulatory volume and tissue perfusion,
  • reducing blood glucose and serum osmolality toward normal levels,
  • clearing ketones from serum and urine at a steady rate,
  • correcting electrolyte imbalances and
  • identifying precipitating factors.
The therapeutic regimen, which consists of replacing fluid and electrolyte losses and administering low-dose insulin, is based on an understanding of the pathogenesis of the condition.

The major treatment of this condition is thus initial rehydration (with isotonic saline) with subsequent potassium replacement and low-dose insulin therapy.

The use of bicarbonate is not recommended in most patients.
• INITIAL REHYDRATION
• The initial priority in the treatment of diabetic ketoacidosis is the restoration of extracellular fluid volume through the intravenous administration of a normal saline (0.9 percent sodium chloride) solution.
• This step will restore intravascular volume, decrease counterregulatory hormones and lower the blood glucose level.
• As a result, insulin sensitivity may be augmented.
• In patients with mild to moderate volume depletion, infusion rates of 7 mL per kg per hour have been as efficacious as infusion rates of 14 mL per kg per hour.10
• The subsequent administration of a hypotonic saline (0.45 percent sodium chloride) solution, which is similar in composition to the fluid lost during osmotic diuresis, leads to gradual replacement of deficits in both intracellular and extracellular compartments.
• When the blood glucose concentration is approximately 250 mg per dL (13.9 mmol per L), glucose should be added to the hydration fluid (i.e., 5 percent dextrose in hypotonic saline solution). This allows continued insulin administration until ketonemia is controlled and also helps to avoid iatrogenic hypoglycemia.

• Another important aspect of rehydration therapy in patients with diabetic ketoacidosis is the replacement of ongoing urinary losses.

• The severity of fluid and sodium deficits is determined primarily by the duration of hyperglycemia, the level of renal function and the patient's fluid intake.
Dehydration can be estimated by clinical examination and by calculating total serum osmolality and the corrected serum sodium concentration.

Total serum osmolality is calculated using the following equation:

1. Measured serum sodium (in mEq per L) + (glucose [in mg per dL] \times 0.18) + (blood urea nitrogen [in mg per dL] \times 2.8).

The measured serum sodium concentration can be corrected for the changes related to hyperglycemia by adding 1.6 mEq per L (1.6 mmol per L) to the measured sodium value for every 100 mg per dL (5.6 mmol per L) over the normal baseline of 100 mg per dL.]

Corrected serum sodium concentrations of greater than 140 mEq per L (140 mmol per L) and calculated total osmolalities of greater than 330 mOsm per kg of water are associated with large fluid deficits. Calculated total osmolalities are correlated with mental status, in that stupor and coma typically occur with an osmolality of greater than 330 mOsm per kg of water.
• Insulin Therapy
• Modern management of diabetic ketoacidosis has emphasized the use of lower doses of insulin. This has been shown to be the most efficacious treatment in both children and adults with diabetic ketoacidosis. The current recommendation is to give low-dose (short-acting regular) insulin after the diagnosis of diabetic ketoacidosis has been confirmed by laboratory tests and fluid replacement has been initiated.

• It is prudent to withhold insulin therapy until the serum potassium concentration has been determined. In the rare patient who presents with hypokalemia, insulin therapy may worsen the hypokalemia and precipitate life-threatening cardiac arrhythmias.

• Standard low-dose insulin therapy consists of an initial intravenous bolus of 0.15 U of regular insulin per kg followed by the continuous intravenous infusion of regular insulin prepared in normal saline or hypotonic saline solution at a rate of 0.1 U per kg per hour.
• In clinical situations in which continuous intravenous insulin cannot be administered, the recommended initial insulin dose is 0.3 U per kg, with one half of the dose given as an intravenous bolus and the remainder given subcutaneously or intramuscularly (Figure 2).

• Subsequently, regular insulin should be given in a dosage of 0.1 U per kg per hour until the blood glucose level is approximately 250 mg per dL.

• If the blood glucose concentration does not fall by 50 to 70 mg per dL (2.8 to 3.9 mmol per L) in the first hour, the intravenous infusion rate should be doubled or additional intravenous 10-U boluses of insulin should be given every hour (Figure 2).

• **Either of these treatments should be continued until the blood glucose level falls by 50 to 70 mg per dL. Low-dose insulin therapy typically produces a linear fall in the glucose concentration of 50 to 70 mg per dL per hour.**12
• More rapid correction of hyperglycemia should be avoided because it may increase the risk of cerebral edema.
• This dreaded treatment complication occurs in approximately 1 percent of children with diabetic ketoacidosis.
• The typical presentation is onset of headache and decreased mental status occurring several hours after the start of treatment.
• Cerebral edema is associated with a mortality rate of up to 70 percent.15
• When a blood glucose concentration of 250 mg per dL has been achieved, the continuous or hourly insulin dosage can be reduced to 0.05 U per kg per hour. **The insulin and fluid regimens are continued until ketoacidosis is controlled.** This requires the achievement of at least two of these acid-base parameters: a serum bicarbonate concentration of greater than 18 mEq per L, a venous pH equal to or greater than 7.3 and an anion gap of less than 14 mEq per L.
• Potassium Therapy

• Although the typical potassium deficit in diabetic ketoacidosis is 500 to 700 mEq (500 to 700 mmol), most patients are hyperkalemic at the time of diagnosis because of the effects of insulinopenia, hyperosmolality and acidemia.

• During rehydration and insulin therapies for diabetic ketoacidosis, the serum potassium concentration typically declines rapidly as potassium reenters the intracellular compartment.

• One protocol entails using insulin and intravenous fluids until the serum potassium concentration is less than 5.5 mEq per L (5.5 mmol per L).

• At this time, potassium chloride is added to intravenous fluids in the amount of 20 to 40 mEq per L. The exact amount of potassium that is administered depends on the serum potassium concentration. When the serum potassium level is less than 3.3 mEq per L (3.3 mmol per L), the administration of 40 mEq per L of potassium is appropriate. If the serum potassium is greater than 3.3 mEq per L but less than 5.5 mEq per L, 20 to 30 mEq per L of potassium can be administered. The goal is to maintain the serum potassium concentration in the range of 4 to 5 mEq per L (4 to 5 mmol per L).1,2,6
Bicarbonate Therapy

In general, supplemental bicarbonate therapy is no longer recommended for patients with diabetic ketoacidosis, because the plasma bicarbonate concentration increases with insulin therapy. Insulin administration inhibits ongoing lipolysis and ketone production and also promotes the regeneration of bicarbonate.

Retrospective reviews and prospective randomized studies have failed to identify changes in morbidity or mortality with sodium bicarbonate therapy in patients who presented with a pH of 6.9 to 7.1. Therefore, the use of bicarbonate in a patient with a pH greater than 7.0 is not recommended. Furthermore, bicarbonate therapy carries some risks, including hypokalemia with overly rapid administration, paradoxic cerebrospinal fluid acidosis and hypoxia.

Some authorities, however, recommend bicarbonate administration when the pH is less than 7.0, for the purpose of treating the possible adverse hemodynamic effects of profound acidemia.

If bicarbonate is used, it should be administered as a nearly isotonic solution, which can be approximated by the addition of one ampule of sodium bicarbonate in 300 mL of sterile water. The bicarbonate solution is given over a one-hour period.

A small percentage of patients with diabetic ketoacidosis present with metabolic acidosis and a normal anion gap. Therefore, they have fewer ketones available for the regeneration of bicarbonate during insulin administration. Bicarbonate therapy may be warranted in this subset of patients.
• **Phosphate Therapy**

• **Osmotic diuresis leads to increased urinary phosphate losses.** During insulin therapy, phosphate reenters the intracellular compartment, leading to mild to moderate reductions in the serum phosphate concentration. Adverse complications of hypophosphatemia are uncommon and occur primarily in patients with severe hypophosphatemia (a serum phosphate concentration of less than 1.0 mg per dL [0.32 mmol per L]).

• **Prospective studies have indicated no clinical benefit for phosphate replacement in the treatment of diabetic ketoacidosis, and excessive phosphate replacement may contribute to hypocalcemia and soft tissue metastatic calcification.**

• **Although the replacement of phosphate per se is not routinely recommended, it may be useful to replace some potassium as potassium phosphate.** One protocol is to administer two thirds of the potassium as potassium chloride and one third as potassium phosphate. The use of phosphate for this purpose reduces the chloride load that might contribute to hyperchloremic acidosis and decreases the likelihood that the patient will develop severe hypophosphatemia during insulin therapy.
Immediate Posthyperglycemic Care

When diabetic ketoacidosis has been controlled, subcutaneous insulin therapy can be started. The half-life of regular insulin is less than 10 minutes. Therefore, to avoid relapse of diabetic ketoacidosis, the first subcutaneous dose of regular insulin should be given at least one hour before intravenous insulin is discontinued.

In patients who are unable to eat, 5 percent dextrose in hypotonic saline solution is continued at a rate of 100 to 200 mL per hour.

Blood glucose levels are monitored every four hours, and regular insulin is given subcutaneously every four hours using a sliding scale. When patients are able to eat, multidose subcutaneous therapy with both regular (short-acting) and intermediate-acting insulin may be given.

In patients with newly diagnosed diabetes, an initial total insulin dosage of 0.6 to 0.7 U per kg per day is usually adequate to achieve metabolic control.

A typical regimen is two thirds of the total daily dosage before breakfast and one third of the total daily dosage before dinner, with the insulin doses consisting of two-thirds NPH (intermediate-acting) insulin and one-third regular (short-acting) insulin.

Patients with known diabetes can typically be given the dosage they were receiving before the onset of diabetic ketoacidosis.
Complications of Therapy

Symptomatic cerebral edema occurs primarily in pediatric patients, particularly those with newly diagnosed diabetes. No single factor predictive for cerebral edema has yet been identified. As noted previously, however, overly rapid rehydration or overcorrection of hyperglycemia appears to increase the risk of cerebral edema.

Onset of headache or mental status changes during therapy should lead to consideration of this complication.

Intravenous mannitol in a dosage of 1 to 2 g per kg given over 15 minutes is the mainstay of therapy. Prompt involvement of a critical care specialist is prudent.
• Adult respiratory distress syndrome (ARDS) is a rare but potentially fatal complication of the treatment of diabetic ketoacidosis. Excessive crystalloid infusion favors the development of pulmonary edema, even in the presence of normal cardiac function. Patients with an increased alveolar to arterial oxygen gradient (AaO2) and patients with pulmonary rales on physical examination may be at increased risk for ARDS. Monitoring of oxygen saturation with pulse oximetry may assist in the management of such patients.

• Hyperchloremic metabolic acidosis with a normal anion gap typically persists after the resolution of ketonemia. This acidosis has no adverse clinical effects and is gradually corrected over the subsequent 24 to 48 hours by enhanced renal acid excretion.\textsuperscript{8,18} The severity of hyperchloremia can be aggravated by excessive chloride administration in hydration fluids.
• Resource Utilization in Diabetic Ketoacidosis

• No randomized prospective studies have evaluated the optimal site of care for patients with diabetic ketoacidosis. The response to initial therapy in the emergency department can be used as a guideline for choosing the most appropriate hospital site (i.e., intensive care unit, step-down unit, general medical ward) for further care.

• Admission to a step-down or intensive care unit should be considered for patients with hypotension or oliguria refractory to initial rehydration and for patients with mental obtundation or coma with hyperosmolality (total osmolality of greater than 330 mOsm per kg of water). Most patients can be treated in step-down units or on general medical wards in which staff members have been trained in on-site blood glucose monitoring and continuous intravenous insulin administration.

• Milder forms of diabetic ketoacidosis can be treated in the emergency department using the same treatment guidelines described in this review.
• Successful outpatient therapy requires the absence of severe intercurrent illness, an alert patient who is able to resume oral intake and the presence of mild diabetic ketoacidosis (pH of greater than 7.2 and a plasma bicarbonate concentration of greater than 10 mEq per L).24

• With the use of standardized written treatment guidelines and flow sheets for monitoring therapeutic response, the mortality rate for patients with diabetic ketoacidosis is now less than 5 percent.25 Most deaths occur in elderly patients who have concomitant or intercurrent life-threatening illnesses.1-4,6 Similar outcomes for the treatment of diabetic ketoacidosis have been observed in both community and training hospitals. These outcomes have not been altered by the specialty of the primary treating physician (e.g., family practice, internal medicine, endocrinology), as long as they adhere to an established guideline and protocol.26
• MANAGEMENT OF HYPOGLYCEMIA

Hypoglycemia may be due to
  – Overshooting in insulin therapy
  – Hypoglycemia from long-acting oral agents

• ****Check net for other causes
• If patient is conscious and can swallow  GIVE THEM A SWEET DRINK
• Glucose administration: give 5-10 g of glucose orally
• For mild reactions: orange juice, glucose, sugar containing beverage, food (assumes patient is conscious)
• If the patient is unconscious or otherwise unable to drink
• For more severe hypoglycemia give 20-50 ml intravenous infusion of 50% w/v glucose solution over a 2-3 minute interval.
• If patient is unconscious and intravenous glucose cannot be administered  GIVE GLUCAGON.
• If intravenous administration of glucose is not feasible or if the patient is comatose, give 1 mg of glucagon (subcutaneous or intramuscular administration) to restore consciousness within about 15 minutes (then allowing food consumption)
• BUT BE AWARE!!!
• That Glucagon causes nausea and vomiting in some patients and, therefore, carries the risk of aspiration in unconscious patients

• NOTE THAT

• Glucagon's main therapeutic use is in the emergency treatment of hypoglycemic coma in insulin-treated diabetic patients.
• It can be given IV for rapid action, but it may also be given IM or subcutaneously.
• Because prolonged hypoglycemia is life-threatening and glucagon is a powerful glucose stimulant, prudent use of glucagon can be life-saving.
• Glucagon is also used to reverse the cardiac effects from an overdose of beta–blockers and as an aid in radiology because of its ability to relax the smooth muscle of the large intestine

• **NOTE Drugs that impair glucose tolerance:**
  • corticosteroids in pharmacologic doses;
  • excessive doses of thyroid hormone;
  • thiazide diuretics;
  • furosemide;
  • combination oral contraceptives;
  • nicotinic acid in pharmacologic doses;
  • propranolol;
  • phenytoin
APPENDIX
DIABETES MELLITUS

• Metabolic disease due to a deficiency of the synthesis or utilization of insulin

• Symptoms and signs

• Polyuria

• Polydipsia

• Polyphagia

• Hyperglycemia

• Glucosuria

• Several complications
**Interpretation of fasting plasma glucose concentration**

<table>
<thead>
<tr>
<th>Glucose Concentration (mmol/L)</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>6.1</td>
<td>impaired fasting glucose</td>
</tr>
<tr>
<td>6.1</td>
<td>normal</td>
</tr>
<tr>
<td>2.5</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>type 1</td>
<td>autoimmune destruction of β-cells</td>
</tr>
<tr>
<td>type 2</td>
<td>β-cell failure and insulin resistance</td>
</tr>
<tr>
<td>other types</td>
<td>genetic defects of β-cells (e.g. mutations of glucokinase gene). Rare insulin resistance syndromes. Diseases of exocrine pancreas. Endocrine diseases (acromegaly, Cushing's syndrome). Drugs and chemical-induced diabetes. Infections (e.g. mumps). Rare syndromes with the presence of antireceptor antibodies. Diabetes accompanying other genetic diseases (e.g. Down syndrome)</td>
</tr>
<tr>
<td>gestational diabetes</td>
<td>any degree of glucose intolerance diagnosed in pregnancy</td>
</tr>
</tbody>
</table>
CLASSIFICATION OF DIABETES MELLITUS

INSULIN DEPENDENT
- Youth
- Thinness
- Ketosis
- Low concentration of insulin
- Insulin

NON INSULIN DEPENDENT
- Adulthood
- Obesity
- Hyperglycemia
- High concentration of insulin
- Diet and oral hypoglycemic drugs
COMPLICATIONS OF DIABETES MELLITUS II

- Hyperglycemia
- Spontaneous glycosylation of proteins
- High concentration of sorbitol
Hemoglobin $A_1c$ measurements

1st visit to the diabetic clinic; the patient has high plasma glucose concentration and high $HbA_1c$ (8%); physician increases insulin dose

2nd visit to the diabetic clinic; the patient has normal plasma glucose level but still increased $HbA_1c$ concentration (7.5%)

Hyperglycemia: formation of excess at $HbA_1c$ takes place

Increased $HbA_1c$ concentration persists over the life span of affected erythrocytes
Interpretation of hemoglobin A$_{1c}$ concentration

- 7%: poor control of diabetes
- 6%: good control of diabetes
- 4%: reference range
Major long term complications of diabetes

Autonomic neuropathy:
diarrhea, impotence

Diabetic foot:
peripheral neuropathy
and ischemia, foot ulcers,
amputations

Retinopathy:
visual impairment
and blindness

Macroangiopathy:
coronary heart disease
peripheral vascular disease

Nephropathy:
renal failure

Assessment of a diabetic patient
- blood glucose and HbA1c
- eye examination
- serum creatinine, urine protein
- microalbuminuria
- neurologic examination
- ECG
- serum lipid levels
### Comparison of type 1 and type 2 diabetes mellitus

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>usually below 20 years of age</td>
<td>usually over 40 years of age</td>
</tr>
<tr>
<td><strong>Insulin synthesis</strong></td>
<td>absent: immune destruction of β-cells</td>
<td>preserved: combination of impaired β-cell function and insulin resistance</td>
</tr>
<tr>
<td><strong>Plasma insulin concentration</strong></td>
<td>low or absent</td>
<td>low, normal, or high</td>
</tr>
<tr>
<td><strong>Genetic susceptibility</strong></td>
<td>yes, inheritance associated with HLA antigens</td>
<td>not associated with HLA, important polygenic inheritance</td>
</tr>
<tr>
<td><strong>Islet cell antibodies at diagnosis</strong></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>uncommon</td>
<td>common</td>
</tr>
<tr>
<td><strong>Ketoacidosis</strong></td>
<td>yes</td>
<td>possible after major stress</td>
</tr>
</tbody>
</table>