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.
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 KETOACIDODIS.

• 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, **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.
• The acidosis is referred to as a ketoacidosis because it is due to the presence of high levels of ketone bodies resulting from increases in hepatic ketone body synthesis and release
• 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

Amino acids

Pyruvate → Oxaloacetate → Acetyl-CoA

Fatty acids → HS-CoA → Ketone bodies

Acetyl-CoA → Krebs Cycle

Respiratory chain → Energy

Krebs Cycle

Energy
DIABETIC KETOACIDOSIS

Insulin lack

- Increased gluconeogenesis
  - Hyperglycemia
    - Glycosuria
      - Osmotic diuresis
        - Dehydration

- Increased lipolysis
  - Increased ketogenesis
    - Hyperketonemia
      - ketonuria
      - Acidosis
        - Hyperventilation
DIABETES - an addendum
METABOLIC MODIFICATIONS IN DIABETES MELLITUS
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
<table>
<thead>
<tr>
<th>Glucose Concentration (mmol/L)</th>
<th>Interpretation</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>
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</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\textsubscript{1c} measurements

1st visit to the diabetic clinic; the patient has high plasma glucose concentration and high HbA\textsubscript{1c} (8%); physician increases insulin dose

2nd visit to the diabetic clinic; the patient has normal plasma glucose level but still increased HbA\textsubscript{1c} concentration (7.5%)

Hyperglycemia: formation of excess at HbA\textsubscript{1c} takes place

increased HbA\textsubscript{1c} concentration persists over the life span of affected erythrocytes

hemoglobin

glucose

HbA\textsubscript{1c}
Interpretation of hemoglobin A₁c 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
<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>usually below 20 years of age</td>
<td>usually over 40 years of age</td>
</tr>
<tr>
<td>Insulin synthesis</td>
<td>absent: immune destruction of β-cells</td>
<td>preserved: combination of impaired β-cell function and insulin resistance</td>
</tr>
<tr>
<td>Plasma insulin concentration</td>
<td>low or absent</td>
<td>low, normal, or high</td>
</tr>
<tr>
<td>Genetic susceptibility</td>
<td>yes, inheritance associated with HLA antigens</td>
<td>not associated with HLA, important polygenic inheritance</td>
</tr>
<tr>
<td>Islet cell antibodies at diagnosis</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Obesity</td>
<td>uncommon</td>
<td>common</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>yes</td>
<td>possible after major stress</td>
</tr>
</tbody>
</table>
• How does the presence of ketone bodies in the blood lead to ketoacidosis?
Some interesting questions to consider:

• Define ketone body.
• List the ketone bodies
• Under what conditions are ketone bodies formed?
• Are ketone bodies ever useful?
• What is ketoacidosis?
• What are some symptoms of ketoacidosis?
• What is the clinical significance of ketoacidosis?
• Ketone bodies are metabolic derivatives from acetyl-CoA with a ketone function.

• The ketone bodies are
  • 1- acetone
  • 2-acetoacetate
  • 3- hydroxybutyric acid

• Examination of the chemical structure of the ketone bodies reveals why they are acidic.
• The ketone acids are relatively strong acids and therefore readily dissociate to release H+ ions.
• Note that the term “ketone body” is historical, and that hydroxybutyric acid is NOT an actual ketone. ...........even though it is called a ketone body!
Ketone bodies are metabolic derivatives from acetyl-CoA with a ketone function (carbonyl group)
• WHEN MADE

• Under what conditions are ketone bodies formed?

• Ketone bodies are formed in

• a- fasting or starvation conditions,

• b- uncontrolled diabetes mellitus,

• c- persons on diets that are extremely low in carbohydrates (as with the high-protein diets).
WHERE THEY ARE MADE?

The major site of production of acetoacetate and 3-hydroxybutyrate is the liver.

Ketone bodies are produced in the liver when the amount of acetylCoA exceeds the oxidative capacity of the liver............when there is excess acetylCoA in the blood.
• HOW WE GET THEM

• Ketones are products of incomplete fatty acid oxidation

• They are usually a result of faulty blood glucose balance, as occurs in states such as diabetes, fasting and starvation.

• Normally, when fat and carbohydrate degradation are appropriately balanced, the acetyl CoA formed in fatty acid oxidation enters the citric acid cycle.
• But during high rates of fatty acid oxidation (as occurs in states such as diabetes, fasting and starvation), when carbohydrates are not available to meet energy needs, or are properly utilized, the body breaks down body fat by a process called beta oxidation of fats.

• Under these conditions, when fatty acid degradation predominates, and occurs more rapidly than glycolysis, large and excessive amounts of acetyl-CoA are generated from fatty acids, but little oxaloacetate is generated from pyruvate.
• The large amounts of acetyl-CoA generated exceeds the capacity of the TCA cycle to function, since entry of acetyl CoA into the TCA depends on the availability of oxaloacetate for the condensation reaction that forms citrate to start the TCA.

• But the supply of oxaloacetate is too low to allow all of the acetyl CoA that is made in the increased fat and protein breakdown that accompanies these states to enter the citric acid cycle.

• So this pathway becomes very limited in its function.
• In such circumstances when oxaloacetate levels are too low, oxaloacetate is diverted from entering the citric acid cycle to gluconeogenesis to form glucose and is thus unavailable for condensation with acetyl CoA.

• The excess acetyl CoA from the beta-oxidation pathway or protein degradation is diverted to form the ketone bodies acetone, acetoacetate and β-hydroxybutyrate.
• Ketone bodies are thus produced in the course of breakdown of fatty acids, in states when fatty acid breakdown predominates, because at some point beta oxidation reaches the point where the fatty acid is degraded to the 4-carbon acetoacetyl CoA.

• Acetoacetyl CoA can either:
  • 1- break down further to acetyl CoA,
  • 2- be used for synthesis of cholesterol and its many derivatives, or.
  • 3- be converted to the ketones (acetoacetate (C4), hydroxybutyrate (C4), and acetone (C3), in the process of ketogenesis.

• Ketones themselves may be used as fuel.
• Remember that in order for the acetyl CoA produced by the beta-oxidation of fatty acids to efficiently enter the citric acid cycle, there must be an adequate supply of oxaloacetate, which is most commonly present if carbohydrates are adequately metabolized by glycolysis to produce a steady supply of pyruvate that can be converted to oxaloacetate.
• In diabetes mellitus, where glucose does not enter the cell and cannot be efficiently utilized, or when insufficient insulin is produced, carbohydrate metabolism is limited, because oxaloacetate needed to produce glucose via gluconeogenesis is deficient in quantity.

• Triglycerides then break down to provide the fatty acids and acetyl CoA for use as fuel, with the concomitant formation of ketones, which may be elevated in the blood.

• In severe diabetic ketosis, one may actually detect the smell of acetone coming from the patient.

• Ketones are also elevated in the blood in states of starvation, when the body calls upon its fatty acids (stored as triglycerides) to break down and provide fuel.
Are ketone bodies useful?

• What is the importance of ketone bodies?
• Until a few years ago, ketone bodies were regarded as degradation products of little physiological value.
• However, it is now known that these derivatives of acetyl CoA are important molecules in energy metabolism, and an alternative fuel for cells.
• It is now known that liver mitochondria have the ability to divert excess acetyl CoA from beta oxidation of fatty acids or pyruvate oxidation to produce ketone bodies.
• These ketone bodies can diffuse from the liver mitochondria into the blood and be transported in the blood to peripheral tissues, where they are reconverted into acetyl CoA and enter the TCA in these extrahepatic tissues as an alternative fuel for these cells.
Acetoacetate and β-hydroxybutyrate exported as energy source for heart, skeletal muscle, kidney, and brain.
• Ketone bodies
• are an important source of energy for peripheral tissues because:
  • they are soluble in aqueous medium – no lipoprotein incorporation or albumin transport is necessary
  • they are therefore used in extrahepatic tissues such as the skeletal and cardiac muscle and renal cortex, in proportion to their concentration in the blood.
• Even the brain can utilize ketone bodies for fuel if the level rises sufficiently. This is important during prolonged periods of fasting.
• Acetoacetate and 3-hydroxybutyrate are normal fuels of respiration and are quantitatively important as sources of energy for some tissues.

• Heart muscle and the renal cortex use acetoacetate in preference to glucose when the ketone bodies concentrations are elevated as a result of fasting.

• Whereas glucose is the major fuel for the brain in well-nourished persons on a balanced diet, the brain adapts to the utilization of acetoacetate during prolonged starvation and diabetes.

• Although the brain normally prefers glucose, in prolonged starvation, the brain adapts to acetoacetate utilization such that 75% of the fuel needs of the brain are met by acetoacetate during states of prolonged starvation.
• In early stages of starvation, when the last remnants of fat are oxidized, heart and skeletal muscle will consume primarily ketone bodies to preserve glucose for use by the brain.

• Acetoacetate and β-hydroxybutyrate, in particular, also serve as major substrates for the biosynthesis of neonatal cerebral lipids.
During prolonged periods of fasting, starvation and diabetes, the brain adapts to the utilization of acetoacetate as fuel for nervous tissue if the level rises sufficiently.

RBCs do not use ketone bodies for fuel simply because mature RBC’s don’t have mitochondria to metabolize acetyl CoA in the TCA.

The liver does not use ketone bodies for fuel, because the liver lacks the enzyme \( \beta \)-ketoacyl-CoA transferase, and therefore little ability to convert acetoacetate into acetyl-CoA.
• Lack of this enzyme in the liver prevents the futile cycle of synthesis and breakdown of acetoacetate.
• The b-ketoacyl-CoA transferase uses succinyl-CoA as the CoA donor, forming succinate and acetoacetyl-CoA.
• This reaction bypasses the succinyl-CoA synthetase step of the TCA cycle, although it does not alter the amount of carbon in the cycle.
• This implies that the TCA cycle must be running to allow ketone body utilization; a fact which is necessarily true, because the TCA cycle is necessary to allow generation of energy from acetyl-CoA
The brain is an important organ. It is metabolically active and metabolically privileged.

The brain generally uses 60-70% of total body glucose requirements, and always requires some glucose for normal functioning.

Under most conditions, glucose is essentially the sole energy source of the brain.

The brain cannot use fatty acids, which cannot cross the blood-brain barrier.

Because animals cannot synthesize significant amounts of glucose from fatty acids, as glucose availability decreases, the brain is forced to use either amino acids or ketone bodies for fuel.

Individuals eating diets extremely high in fat and low in carbohydrates, or starving, or suffering from a severe lack of insulin (Type I diabetes mellitus) therefore increase the synthesis and utilization of ketone bodies.
• What is ketoacidosis?
• What are some symptoms of ketoacidosis?
• What is the clinical significance of ketoacidosis?
• What is ketoacidosis?
• Ketosis refers to the presence of abnormally high levels of blood ketone bodies in the blood, that arises under pathological conditions such as starvation, prolonged fasting, or diabetes.
When fatty acid oxidation in the liver is uncontrolled, as in severe diabetes or starvation, ketone body production becomes excessive and life-threatening, because when ketone bodies accumulate, they may not be completely metabolized by the body. And so there are elevated levels of ketone bodies in the blood.

Under these conditions the blood pH becomes acidic, and can lead to death due to ketosis or ketoacidosis, which can often be detected by the odor of acetone on the breath.

Because two of the ketone bodies are acids, they can lower the blood pH below 7.4, which is acidosis, a condition that often accompanies ketosis.

A drop in blood pH can interfere with the ability of the blood to carry oxygen and cause breathing difficulties.
• Both b-hydroxybutyrate and acetoacetate are organic acids. These compounds are released in the protonated form, which means that their release tends to lower the pH of the blood.

• In normal individuals, other mechanisms compensate for the increased proton release, but individuals with untreated Type I diabetes mellitus often release ketone bodies in such large quantities that the normal pH-buffering mechanisms are overloaded!

• Under such conditions; the reduced pH, in combination with a number of other metabolic abnormalities associated with lack of insulin results in diabetic ketoacidosis, a life-threatening acute disorder of Type I diabetes.

• In most cases, the increase in ketone body concentration in blood is due to increased synthesis in liver; in severe ketoacidosis, cells begin to lose ability to use ketone bodies also.
• Why does ketosis or ketoacidosis occur with the very high concentration of ketone acids in the blood that accompanies diabetes, or starvation?

• Ketones are commonly elevated in the blood in states of diabetes, or starvation, as the body calls upon its fatty acids (stored as triglycerides) to break down and provide fuel.

• Ketones may also be elevated in diabetes mellitus, where glucose does not enter the cell and cannot be efficiently utilized.

• In these states the body breaks down triglycerides to provide the fatty acids and acetyl CoA useful as fuel, sometimes with formation of ketones as well.

• In severe diabetic ketosis, one may actually detect the smell of acetone coming from the patient, as mentioned before.
Ketogenesis

- Ketones are products of incomplete fatty acid oxidation
- Usually a result of faulty blood glucose balance

Low CHO intake, insufficient insulin → Fatty acids flood the liver → Many Acetyl-CoA, Limited Acetyl-CoA → Acetyl-CoA
Ketogenesis in Fasting

- Insulin production falls
- Fatty acids flood the bloodstream
- Oxaloacetate is needed to produce glucose
- Citric Acid Cycle is limited
- More ketones produced

Fasting -- no CHO intake, insufficient insulin

Fatty acids flood the liver

Many Acetyl-CoA

Limited Acetyl-CoA

Acetyl-CoA

Ketones, Citric Acid Cycle
Ketogenesis in Diabetes

- Insufficient insulin produced
- CHO metabolism is limited
- Oxaloacetate is needed to produce glucose
- Citric Acid Cycle is limited
- More ketones produced; ketones spill into urine
- Blood becomes acidic

Insufficient insulin

Fatty acids flood the liver

Many Acetyl-CoA

Limited Acetyl-CoA

Acetyl-CoA

Urine
Catabolism during Fasting

Fasting (↓ insulin, ↑ glucagon)

- Glycogenolysis
- Gluconeogenesis

Liver

Glycogen → Glucose 6-phosphate → Glucose

Pyruvic acid → Acetyl CoA → Ketone bodies

Adipose tissue

Fatty acids → Ketone bodies → Amino acids

Glucose

Skeletal muscle
Effect of Feeding and Fasting on Metabolism

Absorption of meal (↑ Glucose)
- ↑ Insulin
- ↓ Glucagon
- ↑ Insulin/glucagon ratio
  - Formation of glycogen, fat, and protein
  - Blood
    - Glucose
    - Amino acids
    - Fatty acids
    - Ketone bodies

Fasting (↓ Glucose)
- ↓ Insulin
- ↑ Glucagon
- ↓ Insulin/glucagon ratio
  - Hydolysis of glycogen, fat, and protein + Gluconeogenesis and ketogenesis
  - Blood
    - Glucose
    - Amino acids
    - Fatty acids
    - Ketone bodies