8.2: Ketoacidosis

8.2.1: What is ketoacidosis?

Ketoacidosis is a high anion gap metabolic acidosis due to an excessive blood concentration of ketone bodies (ketooanions). Ketone bodies (acetoacetate, beta-hydroxybutyrate, acetone) are released into the blood from the liver when hepatic lipid metabolism has changed to a state of increased ketogenesis. A relative or absolute insulin deficiency is present in all cases. The major reactions starting from the production of acetoacetate from hepatic acetyl CoA are outlined in the box.

Reactions in Ketoacidosis

Note:

- There is one $H^+$ produced for each acid anion produced
- Buffering results in the loss of one $HCO_3^-$ for each $H^+$ buffered
Therefore one predicts that:

Increase in Anion Gap = Decrease in $[\text{HCO}_3^-]$ 

The major ketone bodies are acetoacetate and beta-hydroxybutyrate and the ratio between these two acid anions depends on the prevailing redox state (eg as assessed by the NADH/NAD$^+$ ratio).

A mixed acid-base disorder may be present (eg lactic acidosis from peripheral circulatory failure, or metabolic alkalosis from vomiting). An associated lactic acidosis may mask the presence of the ketoacidosis. This occurs because the lactic acidosis decreases the acetoacetate : beta-hydroxybutyrate ratio (ie more beta-hydroxybutyrate produced ) because NAD$^+$ is produced in the production of lactate. The common test used to detect ketones (eg Acetest) depends on the reaction of acetoacetate (and to a lesser extent acetone) with the nitroprusside reagent. A decreased acetoacetate level may lead to a weak or absent test reaction despite high total levels of total ketoanions (acetoacetate and beta-hydroxybutyrate combined) because the beta-hydroxybutyrate is not detected.

Outline of Interaction between Lactic Acidosis and Ketoacidosis

diagram to be added

Note

Increased lactate cause increased beta-OHB and decreased AcAc by Law of Mass Action

The three major types of ketosis are:

- Starvation ketosis
- Alcoholic ketoacidosis
- Diabetic ketoacidosis

8.2.2: Starvation Ketosis

When hepatic glycogen stores are exhausted (e.g. after 12-24 hours of total fasting), the liver produces ketones to provide an energy substrate for peripheral tissues. Ketoacidosis can appear after an overnight fast but it typically requires 3 to 14 days of starvation to reach maximal severity. Typical ketoanion levels are only 1 to 2 mmol/l and this will not much alter the anion gap. The acidosis even with quite prolonged fasting is only ever of mild to moderate severity with ketoanion levels up to a maximum of 3 to 5 mmol/l and plasma pH down to 7.3. This is probably due to the insulin level, which though lower, is still enough to keep the FFA levels less than 1mM. This limits substrate delivery to the liver restraining hepatic ketogenesis. Ketone bodies also stimulate some insulin release from the islets. The anion gap will usually not be much elevated.

8.2.3: Alcoholic Ketoacidosis
Typical Presentation

This typical situation leading to alcoholic ketoacidosis is a chronic alcoholic who has a binge, then stops drinking and has little or no oral food intake. Food intake may be limited because of vomiting. The two key factors are the combination of ethanol and fasting. Presentation is typically a couple of days after the drinking binge has ceased.

Pathophysiology

The poor oral intake results in decreased glycogen stores, a decrease in insulin levels and an increase in glucagon levels. Hepatic metabolism of ethanol to acetaldehyde and then to acetate both involve NAD$^+$ as a cofactor. The NADH/NAD$^+$ ratio rises and this:

- inhibits gluconeogenesis
- favours the production of beta-hydroxybutyrate over acetoacetate

The insulin deficiency results in increased mobilisation of free fatty acids from adipose tissue. The decreased insulin/glucagon ration results in a switch in hepatic metabolism favouring increased beta-oxidation of fatty acids. This results in an increased production of acetylCoA which forms acetoacetate (a keto-acid). (The pathophysiology of the insulin deficiency and the switch in hepatic metabolism is discussed in more detail in DKA section below.)

Other points to note:

- Volume depletion is common and this can result in increased levels of counter-regulatory hormones (eg glucagon)
- Levels of FFA can be high (eg up to 3.5mM) providing plenty of substrate for the altered hepatic lipid metabolism to produce plenty of ketoanions
- GIT symptoms are common (eg nausea, vomiting, abdominal pain, haematemesis, melaena)
- Acidaemia may be severe (eg pH down to 7.0)
- Plasma glucose may be depressed or normal or even elevated
- Magnesium deficiency is not uncommon
- Patients are usually not diabetic

Management

This syndrome is rapidly reversed by administration of glucose and insulin.

This diagnosis is often overlooked. A strong suspicion should be raised in any ill chronic alcoholic with a sweet ketone breath who presents to a hospital Emergency Department. Such patients are often dishevelled, and can be noisy and generally uncooperative.

A mixed acid-base disorder may be present: high anion gap due to ketoacidosis, metabolic alkalosis due to vomiting and a respiratory alkalosis.
8.2.4 Diabetic Ketoacidosis: (DKA)

Pathophysiology

An absolute or relative lack of insulin leads to diabetic metabolic decompensation with hyperglycaemia and ketoacidosis. A precipitating factor (eg infection, stress) which causes an excess of stress hormones (which antagonise the actions of insulin) may be present.

Situations leading to DKA

The most common situations in patients presenting with DKA are:

- Infection as precipitant (30% of cases)
- Treatment non-compliance (20%)
- New diagnosis of diabetes (25%)
- No known precipitating event (25%)

Since the discovery and therapeutic use of insulin, the mortality from DKA has dropped dramatically from 100% to perhaps 2 to 5% in Western countries today. (Lebovitz, 1995)

An outline of the pathophysiology is presented below. The pathogenesis requires two events:

- Increased mobilisation of free fatty acids (FFA) from adipose tissue to the liver
- A switch of hepatic lipid metabolism to ketogenesis

FFA mobilisation is initiated by the effect of absolute or relative insulin deficiency on fat cells. FFA levels can be quite high (eg 2.5 to 3.5 mM). This provides the liver with plenty of substrate. These FFA levels are much less then ketone levels and contribute only a small amount to the metabolic acidosis.

The major switch in hepatic lipid metabolism occurs in response not just to insulin deficiency but additionally to the concomitant rise in levels of the stress hormones (glucagon, corticosteroids, catecholamines, growth hormone). The role of glucagon is the most clearly established. The hepatic effects of a fall in the insulin:glucagon ratio are:

- Increased glycogenolysis
- Increased gluconeogenesis
- Increased ketogenesis

The net effect is an increase in the hepatic output of both ketone bodies and glucose.

Initial Events in Pathophysiology of Diabetic Ketoacidosis (INCOMPLETE)
Why does the major switch in hepatic metabolism occur?

The inhibition of the enzyme acetyl CoA carboxylase is probably the key step. This enzyme is inhibited by increased FFA levels, decreased insulin levels and particularly by the rise in glucagon. All three of these factors are present in DKA. The effect is to decrease the production and level of malonyl CoA. This compound has a central role in the regulation of hepatic fatty acid metabolism as it mediates the reciprocal relationship between fatty acid synthesis and oxidation. It is the first committed intermediate in fatty acid metabolism. Malonyl CoA inhibits fatty acid oxidation by inhibiting carnitine acyltransferase I.

A fall in malonyl CoA levels removes this inhibition resulting in excessive fatty acid oxidation with excessive production of acetyl CoA and excess acetoacetate.

Hyperglycaemia & Ketoacidosis cause most symptoms

Two basic mechanisms underlie the pathophysiology of DKA: hyperglycaemia and ketoacidosis. The above discussion shows how both these problems follow from relative insulin deficiency coupled with stress hormone excess. The problem however is not just of hepatic over-production of glucose and ketones but also of peripheral underutilisation of both glucose and ketones.

Acetoacetic acid (pKa 3.58) and beta-hydroxybutyric acid (pKa 4.70) dissociate producing H⁺ which is buffered by HCO₃⁻ in the blood. For each anion produced there is a loss of one bicarbonate. The increase in the anion gap (representing the increase in the unmeasured acid anions) should approximately equal the decrease in the [HCO₃⁻]. A pure high anion gap metabolic acidosis results.

Development of hyperchloraemic acidosis

In some cases, a hyperchloraemic metabolic acidosis develops: this is most common during the treatment phase. Why
does this occur? Acetoacetate and beta-hydroxybutyrate are moderately strong acids and even at the lowest urinary pH are significantly ionised. They are excreted with a cation (usually Na\(^+\) or K\(^+\)) to maintain electroneutrality. The net effect is the loss of potential bicarbonate equal to the level of urinary ketone body loss. The HCO\(_3^-\) is replaced in the blood by Cl\(^-\) derived from renal reabsorption, gut absorption or (particularly) IV saline administered during treatment. The effect is to cause a rise in plasma [Cl\(^-\)] and the anion gap returns towards normal despite the persistence of the metabolic acidosis. At presentation, both types of acidosis may be present and the elevation in the anion gap will be less than expected for the degree of depression in the bicarbonate level (resulting in Delta ratio < 0.8).

A predominant hyperchloraemic acidosis (defined as a DKA patient with a delta ratio < 0.4) is present in about 10% of patients on arrival at hospital and in about 70% after 8 hours of treatment. Patients who are more severely dehydrated retain more keto-anions and have a lower incidence of hyperchloraemic acidosis.

Administration of large volumes of normal saline in resuscitation of patients with acute DKA promotes continued diuresis (and continued loss of ketone bodies with Na\(^+\) as the cation) and provides plenty of chloride to replace the lost ketoanions. This hyperchloraemic acidosis is slower to resolve because the keto-anions needed for regeneration of bicarbonate have been lost. Patients who have been able to maintain fluid intake during development of their illness are more likely to have a hyperchloraemic acidosis component present on admission.

**Other acid base disorders may be present**

It should not just be assumed that the patient only has a diabetic ketoacidosis. Possible complicating acid-base disorders are:

- Lactic acidosis due to hypoperfusion and anaerobic muscle metabolism
- Metabolic alkalosis secondary to excessive vomiting
- Respiratory acidosis due to pneumonia or mental obtundation
- Respiratory alkalosis with sepsis
- Renal tubular acidosis (type 4)

Renal tubular acidosis (type 4) is present in some diabetic patients and the associated urinary acidification defect can cause a hyperchloraemic normal anion gap acidosis. This syndrome (known as hyporeninemic hypoaldosteronism) occurs in some elderly diabetics who have pre-existing moderate renal insufficiency but is not a common problem in acute DKA.

**Summary of Events in Pathophysiology of DKA**

- First: A precipitating event occurs which results in insulin deficiency (absolute or relative) and usually an excess of stress hormones (particularly glucagon)
- Hyperglycaemia occurs due to decreased glucose uptake in fat and muscle cells (due to insulin deficiency)
- Lipolysis in fat cells now occurs promoted by the insulin deficiency releasing FFA into the blood
- Elevated FFA levels provide substrate to the liver
- A switch in hepatic lipid metabolism occurs due to the insulin deficiency and the glucagon excess, so
the excess FFA is metabolised resulting in excess production of acetyl CoA.

- The excess hepatic acetyl CoA is converted to acetoacetate (a keto-acid) which is released into the blood
- Ketoacidosis and hyperglycaemia both occur due to the lack of insulin and the increase in glucagon and most of the clinical effects follow from these two factors
- Other acid-base and electrolyte disorders may develop as a consequence and complicate the clinical condition

8.2.5: Management of DKA

An outline of management is presented: this should be tailored to individual circumstances. Management of DKA has passed through 3 stages in the last 100 years:

- Stage 1: Preinsulin era (Feature: mortality of 100%)
- Stage 2: High dose insulin regime (Feature: mortality down to 10% but metabolic complications due to the treatment)
- Stage 3 (the present): Low dose insulin regime (Feature: low mortality)

Mortality with the low dose insulin regime is down to about 2 to 5% overall. In older patients with DKA precipitated by a major medical illness (eg acute pancreatitis, myocardial infarction, septicaemia), the mortality rate is still high due to the severity of the precipitating problem.

Overall aims of treatment

- Replace fluid and electrolyte losses
- Restore normal carbohydrate and lipid metabolism
- Treat the underlying cause
- Manage specific complications

Management can be considered in terms of emergency and routine components.

Emergency Management

A: Airway

- Protect by intubation with a cuffed tube if patient is significantly obtunded.
- Consider placing a nasogastric tube in all patients.

B: Breathing

- Oxygen by mask initially in all patients
• Intubation may be necessary for airway protection or ventilation (e.g., if aspiration, coma, pneumonia, pulmonary oedema, acute pancreatitis, and ARDS) but this is not common.

Special Danger in Ventilated Patients

Maintain compensatory hyperventilation in intubated patients

Patients with metabolic acidosis (e.g., severe DKA) have marked hyperventilation (i.e., respiratory compensation, Kussmaul respirations) and typically low arterial pCO₂ levels. If intubated and ventilated, ventilatory parameters (tidal volume and rate) need to be set to continue a high minute ventilation. If this is not done and pCO₂ is inappropriately high, a severe acidaemia and consequent severe cardiovascular collapse may occur.

This is a particular problem in all situations where a patient with a compensated metabolic acidosis is intubated and ventilated. The rule of thumb is to aim for a pCO₂ level of 1.5 times the bicarbonate level plus eight as this mimics the normal response by the body. As bicarbonate levels recover, adjust ventilation downwards.

C: Circulation

• If shock is present, this requires urgent colloid infusion to restore intravascular volume and tissue perfusion
• Arrhythmias require urgent clinical management dependent on the type and the clinical situation (e.g., hyperkalaemia, myocardial infarction)
• The typical patient who presents with poor peripheral perfusion but normotension can be adequately managed initially with ECF replacement fluids (e.g., Hartmann’s solution or Normal saline)

Other Specific Emergency Treatment

Cerebral oedema is a dangerous complication that occurs in about 1% of children and adolescents with DKA.

Onset of headache and deteriorating level of consciousness typically occurs between 2 and 24 hours after onset of treatment. Onset of symptoms is often sudden. Mortality is about 70% in this group.

Recommended treatment is immediate IV mannitol in a dose of 0.5 to 2.0 g/kg body weight. Dexamethasone or hyperventilation have no proven benefit. (Lebovitz, 1995)
DKA : Routine Management

1. General

- Oxygen by mask
- Urinary catheter
- Consider low dose calcium heparin to decrease risk of arterial thrombosis
- Investigate for underlying illness (history, examination, cultures of blood, urine or sputum, chest xray, ECG etc)

2. Fluids

Immediate aim is to restore intravascular volume to improve tissue perfusion.

Replacement solutions (eg Normal saline or Hartmann's solution) are appropriate for initial management. Subsequently fluids need to be adjusted to provide free water to replenish intracellular fluid and to provide glucose. Maintenance fluids such as dextrose-saline or oral fluid intake are appropriate at this later stage depending on the individual circumstances but such solutions should not be used initially.

Colloids are necessary only in shocked patients. Colloids are expensive and have a low but significant risk of reactions. Albumin solutions are not required.

3. Potassium

Serum level is commonly normal or high (due to the acidosis) at presentation despite the presence of a large total body potassium deficit (due to renal losses). The best approach is to commence therapy with fluid and insulin and monitor the serum $[K^+]$.

Potassium replacement can be commenced when the $[K^+]$ falls below 5 mmols/l. Infuse at 10 to 30 mmol/hr dependent on $[K^+]$. Rates greater than 20 mmols/hr are reserved for severe hypokalaemia and require at least hourly $[K^+]$ monitoring. Never commence a potassium infusion without checking the level.

4. Insulin

Fluid resuscitation is necessary to deliver insulin to its sites of action in liver, muscle and adipose tissue. Rehydration itself will cause a fall in blood glucose level.

A typical regime would be to give a stat dose initially (say 10-20U IV) and commence the patient on a continuous insulin infusion at 5 to 10 U/hr decreasing to 1-3 U/hr to maintain blood glucose at 5 to 10 mmols/l. A paediatric regime would be: insulin at 0.1U/kg IV loading dose then infusion at 0.1U/kg/hr.

The blood glucose always falls on this regime and control of blood glucose is almost never a problem. Insulin reverses the peripheral mobilisation of FFA and alters hepatic metabolism to switch off ketone body production. These effects are maximal at insulin levels of 100 micromoles/l and this level is achieved with the low dose regime. The average rate of fall of plasma glucose at this insulin level is about 4.5 mmol/l/hr. There is no advantage in giving more insulin once the
ceiling level is reached. This absence of additional effectiveness with very high insulin levels has been referred to in the past as _insulin resistance_.

### 5. Phosphate

Though a total body deficiency is always present, it has not been possible to show that acute phosphate administration makes any difference to outcome. However the occasional patient develops extremely low phosphate levels and phosphate administration is undoubtedly necessary in these patients and must be given. Phosphate level on presentation is typically high so phosphate administration should be delayed.

By twelve hours after commencement of treatment, the majority (90%) of patients are hypophosphataemic. Ampoules of phosphate available in my hospital contain about 15 mmoles of phosphate and 20 mmoles of potassium and one ampoule can be diluted in the IV fluids and infused over an hour.

### 6. Bicarbonate

Sodium bicarbonate in DKA has arguably a minor role is in urgent management of serious arrhythmias due to hyperkalaemia in DKA. However, glucose-insulin is the preferred treatment in this patient group.

None of the studies done in DKA have shown any benefit of bicarbonate treatment. Potential problems are sodium overload, CSF acidosis, intracellular acidosis, exacerbation of hypokalaemia, rebound alkalosis and impaired tissue oxygen delivery (shift of oxyhaemoglobin dissociation curve). After treatment of DKA starts, the slowest biochemical parameter to recover is usually the serum bicarbonate - this is especially so when substantial amounts of ketones have been lost in the urine. New bicarbonate is generated when the condition is reversed and the ketones are metabolised. Bicarbonate administration is not necessary.

### 7. Monitoring

Management in an Intensive Care Unit is recommended.

Monitoring should include observations of airway, breathing, circulation and level of consciousness, serial blood gases and electrolytes, urinary ketones and urine output. Serum lactate is occasionally useful. A Biochemistry Flowchart of results is strongly recommended.

**Cerebral oedema presents 2 to 12 hours after start of treatment**

Cerebral oedema is the commonest single cause of mortality, particularly in children. It typically develops after treatment has commenced. A headache or decreasing level of consciousness are the usual initial sign. Onset may be sudden. Treat urgently with IV mannitol. Intubation for airway protection may be required. Maintain hyperventilation in ventilated patients.

### 8. Treat the Underlying Cause

The commonest precipitants in young diabetics are inadequate insulin (eg first presentation of diabetes, omission of doses) and infection. Often no specific cause can be found. In older diabetics, DKA may be precipitated by a major medical illness (esp infection). Antibiotics or surgical management are necessary in some cases. Patient education to
prevent further episodes is very important.