diabetic ketoacidosis [created by Paul Young 15/12/07]

general

- Ketoacidosis is a high anion gap metabolic acidosis due to an excessive blood concentration of ketone bodies (keto-anions).
- 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.

causes

The three major types of ketosis are:
(i) Starvation ketosis
(ii) Alcoholic ketoacidosis
(iii) Diabetic ketoacidosis

relationship between lactic acidosis and ketoacidosis

- 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 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).
- 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.

starvation ketosis

- When hepatic glycogen stores are exhausted (eg 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 usually not 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.

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. 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:
(i) inhibits gluconeogenesis
(ii) 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).

Other features
- 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.
- A mixed acid-base disorder may be present: high anion gap due to ketoacidosis, metabolic alkalosis due to vomiting and a respiratory alkalosis.

General:
- involves 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.
- The most common situations in patients presenting with DKA are:
(i) Infection as precipitant (30% of cases)
(ii) Treatment non-compliance (20%)
(iii) New diagnosis of diabetes (25%)
(iv) No known precipitating event (25%)

Pathophysiology
- The pathogenesis requires two events:
(i) Increased mobilisation of free fatty acids (FFA) from adipose tissue to the liver
- 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.
(ii) A switch of hepatic lipid metabolism to ketogenesis
- 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 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.
- 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 is 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.
- The problem however is not just of hepatic over-production of glucose and ketones but also of peripheral underutilisation of both glucose and ketones.

Development of high anion gap acidosis in DKA
- 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. This occurs because 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.

Mixed 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. 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
- 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.

Other acid base disorders in DKA
- Possible complicating acid-base disorders are:
(i) Lactic acidosis due to hypoperfusion and anaerobic muscle metabolism
(ii) Metabolic alkalosis secondary to excessive vomiting
(iii) Respiratory acidosis due to pneumonia or mental obtundation
(iv) Respiratory alkalosis with sepsis
(v) 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