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 glycolysis, 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 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 increased 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 hypochloraemic acidosis
- In some cases, a hypochloracetic metabolic acidosis develops: this is most common during the treatment phase. This occurs because acetacetate 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 hyperchloacetic 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 hyperchloacetic acidosis. Patients who have been able to maintain fluid intake during development of their illness are more likely to have a hyperchloacetic 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 ketonians.

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 hyperchloacetic normal anion gap acidosis. This syndrome (known as hyperoneminic hypoaacidostonemia) occurs in some elderly diabetics who have pre-existing moderate renal insufficiency but is not a common problem in acute DKA.