What are ketones?
Ketone bodies are energy-rich molecules, derived from fat, which can be utilized by tissues during periods of glucose deficiency. They are short-chain organic acids that can freely move across cell membranes, even the bloodbrain barrier (BBB). Therefore, ketones play a crucial role in providing energy to the brain, which unlike other tissues cannot use fatty acids.

At physiologic pH, these organic acids dissociate completely and when present in large quantities, may lead to a metabolic acidosis with high anion gap.

Why should we measure β–OHB?
Beta–OHB and AcAc are normally produced in a 1:1 ratio. However, this ratio increases according to the redox potential in the hepatic mitochondria. During DKA, the highly reduced state of the mitochondria results in higher production of β–OHB and the ratio increases, sometimes to as high as 10:1. In the event of sudden insulin deficiency, blood levels of β–OHB therefore increases rapidly, while the urinary excretion of AcAc is not only decreased, but also delayed, as it is dependent on renal function and hydration status.

During recovery, the redox potential changes and relatively more AcAc is produced and excreted.

Unfortunately, the widely used urine dipstix test for ketones only detects AcAc, resulting in a false impression of the ketone status of the patient: During acute DKA, ketosis is underestimated and during recovery, overestimation of ketosis may lead to inappropriate treatment.

What causes ketosis?
Mild to moderate elevation in serum levels of ketones is a physiological response to fasting, (especially during infancy and pregnancy), prolonged exercise, or a ketogenic (high-fat, low-carbohydrate) diet.

Pathological causes of ketosis include diabetes mellitus (DM), cortisol deficiency, growth hormone deficiency, toxic ingestion of ethanol or salicylates, and certain rare inborn errors of metabolism.

Serum levels of ketones are normally <0.5 mmol/L. Hyperketonaemia can be defined as levels >1 mmol/L. Ketoacidosis is probable above 3.0 mmol/L.

Other disadvantages of the urine ketone test are false positive results in the presence of drugs containing sulhydryl groups (such as Captopril®, penicillamine, mesna) and false negative results may be obtained with highly acidic urine specimens, such as after ingestion of large quantities of ascorbic acid. The urine ketones test is also not quantitative and subject to correct interpretation.
A new blood test is now available for quantitative measurement of β–OBH

How can β–OHB be used?

Diagnosis and treatment of DKA:
Criteria for diagnosing DKA include serum bicarbonates ≤ 18 mmol/L, pH ≤ 7.3, anion gap >10 mmol/L, plasma glucose >13.9 mmol/L and the presence of ketonuria or ketonaemia. However, these criteria have limitations, as the bicarbonate, pH and anion gap may be affected by co-existing acid-base disturbances, e.g. chronic renal disease, respiratory disease, vomiting, lactic acidosis.

Measurement of β–OHB, on the other hand, directly reflects the rate of ketone body production, which is accompanied by an equimolar production of hydrogen ions.¹

A β–OHB level of ≥3 mmol/L predicts the presence of DKA with a likelihood ratio of 15. In contrast, the best predictive value with urine dipstix of 3+ ketones, is a likelihood ratio of 6.³

βOHB levels correlate better with the changes in acid-base status during the course of treatment for DKA. It was found that when insulin therapy adjustment was based on β–OHB instead of glucose levels, the resolution of ketosis occurred 14 hours earlier.²

In summary:

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References:
4. Taboulet, P. Diabetes & Metabolism 2007; (33):135-139

Compiled by Dr Esmé Hitchcock, Chemical Pathologist, PathCare Cape Town

Home-monitoring:
An instrument is also available for measurement of capillary (finger-prick) blood β–OHB, which can be used by patients at home. Monitoring β–OHB, with adequate supplemental insulin, may reduce or even prevent the occurrence of DKA episodes, compared to ketonuria guidelines, especially in children with Type 1 DM.