KETONES

Ketones are produced in the liver, mainly from the oxidation of fatty acids, and are exported to peripheral tissues for use as an energy source. They are particularly important for the brain, which has no other substantial non-glucose-derived energy source. The presence of ketones in the urine implies:

a) that lipid energy metabolism has been activated, and,
b) that the entire pathway of lipid utilization is intact.

Ketosis is normal: during fasting, after prolonged exercise, and when a high fat, low carb diet is consumed.

Ketosis is pathological: in diabetes, ketotic hypoglycemia of childhood, corticosteroid deficiency, growth hormone deficiency, alcohol or salicylate intoxication, inborn error of metabolism

The absence of ketosis in a patient with hypoglycemia is abnormal, and suggests either hyperinsulinism or an inborn error of fat energy metabolism.

There are 6 common instances in which you will find ketones in a patient's urine (actually there are 7 --- with the 7th being an advanced stage alcoholic, but you probably do not encounter too many of those in your practice.)

a) Patients with no particular Metabolic Imbalance who are either fasting, or on an ultra low carb diet.

b) Type I/Insulin Dependent Diabetics whose sugar is borderline out of control.

c) Dysaerobic Imbalance

d) Ketogenic Imbalance

e) Sympathetic Imbalance

f) Metabolic or Respiratory Alkalosis Imbalance

Ketones in the urine are manifestations of Metabolic Imbalances in patients with Dysaerobic, Ketogenic, Sympathetic, Acidosis and Alkalosis Imbalances.

Ketones appear in the urine as an indication of good progress when you are treating Anaerobic, Glucogenic, and Parasympathetic Imbalances.

Ketones in the urine upon initial testing rules out an Anaerobic or Parasympathetic Imbalance in that patient.

Role of the liver in maintenance of [glucose]:

- breakdown of hepatic glycogen

- gluconeogenesis from:
    - lactate (= best precursor to liver gluconeogenesis)
    - amino acids (alanine, glutamine)
    - glycerol
    - pyruvate

Breakdown of hepatic glycogen and gluconeogenesis contribute about equally in the overnight fasted state. After a 36-48 hour fast, hepatic glycogen stores are depleted, but gluconeogenesis continues.

Short term intense exercise: hepatic glycogenolysis is the primary source of extra glucose for muscle

Intermediate term intense exercise: Cori Cycle = muscle lactate → to the liver = gluconeogenesis = glucose → recycled to muscle

Long term exercise: hepatic gluconeogenesis assumes an ever greater role as insulin falls and glucagon rises

Type I Diabetes = decreased hepatic glycogen stores, increased gluconeogenesis, and increased basal hepatic glucose production

Type II Diabetes = hyperglycemia associated in part with accelerated gluconeogenesis

Carbohydrate restriction = in subjects on weight loss diets = gluconeogenesis comes mostly from lactate and amino acids (protein catabolism), not glycerol, even though there is increased fat oxidation. Reliance on the Krebs cycle is attenuated, with increased reliance on hepatic beta-oxidation of fatty acids.

The kinetics of ketone bodies are the same, whether the ketosis is due to Type I Diabetes or to fasting:

- There is a progressive limitation in the ability of tissues to remove ketones from the blood as the [ketone] rises.

- There is also a negative feedback from circulating ketones on the rate of ketogenesis during fasting = prevents the development of uncontrolled hyperketonemia during starvation.

Norepinephrine (and dopamine) causes hyperketonemia in three ways:

- increased catabolism of fats = ketone body production from augmented Free Fatty Acid supply to the liver
- accelerates hepatic ketogenesis
- moderately decreases metabolic clearance of ketone bodies

Type I Diabetic Acute insulin deficiency augments all three effects, resulting in progressive ketosis.

Cortisol in response to stress = increases [glucose] and increases gluconeogenic precursors (except glycerol), but also increases insulin, which limits lipolysis and ketosis. However, if there is also insulin deficiency (= Sympathetic Imbalance or Type 1 Diabetes), glucocorticoids will increase ketosis.

Hyperthyroid = Respiratory Quotient (RQ) unchanged = the increased oxidation comes equally from lipid-derived and carb-derived fuel --- but --- the increase in lipid fuel oxidation does cause ketosis and increased [glycerol].

Metabolic Alkalosis = enhances ketone production. Intravenous infusion of sodium bicarbonate = blood ketones of ketotic rats increase, and urinary ketones increase.

Metabolic Acidosis = (except in Type 1 Diabetic Keto-Acidosis) inhibits ketone production. Intravenous infusion of hydrochloric acid = blood ketones of ketotic rats decrease 1.9 mM, and urinary ketones decrease 1.3 mumol/min.

Respiratory Alkalosis (hypocapnia) = blood and urine ketones increase

Respiratory Acidosis (hypercapnia) = blood ketones of ketotic rats decrease 1.1 mM.

Keto-ALKALOSIS in diabetics = depletion of H^+, Cl^-, and K^+

Nicotinic acid reverses ketosis by lowering the level of c-AMP.

KETONES IN URINE = DYSAEROBIC, SYMPATHETIC, INSULIN DEFICIENCY, GLUCOGENIC WITH SYMPATHETIC COMPENSATION, KETOGENIC, ALKALOSIS, CORTICOSTEROID DEFICIENCY, GROWTH HORMONE DEFICIENCY, FASTING, EXERCISE, HIGH FAT OR LOW CARB DIET, HYPERTHYROID

Liver production of ketoacids as a compensation for Alkalosis:

- Keto acid production and blood and urinary ketone levels are associated with an Alkalosis.

    - Metabolic Acidosis inhibits and Metabolic Alkalosis enhances keto acid production in ketotic humans and animals.

    - Metabolic Acidosis (intravenous infusion of HCl) = blood ketones of ketotic rats decrease 1.9 mM and urinary ketones decrease 1.3 micro moles/minute.

    - Respiratory Acidosis (hypercapnia) = blood ketones of ketotic rats decreases 1.1 mM.

    - Metabolic Alkalosis (intravenous infusion of NAHC03) = blood ketones of ketotic rats increases and urinary ketones also increase.

    - Respiratory Alkalosis (hypocapnia) = blood and urine ketones of ketotic rats increases.

    - Keto Alkalosis in diabetics = depletion of H+, Cl-, and K+

    - Summary: Modest changes in systemic pH modify ketone production, confirm pH control of endogenous acid production as an acid-base regulator, and show that systemic pH, not bicarbonate production, mediates the process.

LaGrange, et al. Ketoacid production in acute respiratory and metabolic acidosis and alkalosis in rats. Am J Physiol, Mar. 1989

Common question from a NUTRI-SPEC practitioner: "If ketoacidosis leads to increased acidity and subsequent increased breathing rate (via other authors'

statements) and presumably reduced breath hold time, how would they become alkaline?" ----- You are absolutely correct, a ketoacidosis is indeed a type of Metabolic Acidosis, and is accompanied by an increased respiratory rate and decreased breath hold time. In other words, a person in a state of ketoacidosis is extremely acid (not alkaline) and must be treated as an Acidosis.

--- However --- as it turns out, only 1 (actually 2, counting the alcoholics) of the 4 mechanisms listed above for urinary ketone production are associated with a ketoacidosis. 3 of the 4 are associated with a condition that almost no one understands --- a **KETOALKALOSIS.**

It is the Type I Insulin Dependent Diabetics who can, when they are in a near crises state, go into a ketoacidosis. The potentially life-threatening ketoacidosis in diabetics is such a focal point in medical training that virtually no doctors have ever even considered the possibility that most states of ketosis are actually associated with an Alkalosis.

What is the difference between a ketoacidosis of a Type I diabetic and the ketoalkalosis of a patient who is Ketogenic, or who is fasting, or on an ultra low carbohydrate diet? The mechanisms by which a ketoacidosis and a ketoalkalosis are produced are not opposites of each other, they involve entirely different metabolic pathways.

In a diabetic ketoacidosis, the extraordinary volume of ketone bodies produced overwhelms the blood buffers, and overwhelms the kidney acid excretion capacity. The diabetic in a crisis state cannot get sugar into his cells to maintaining normal balance between energy production from glucose and energy production from fats. In desperation, the body starts producing energy entirely by the hydroxybutyrate pathway, with the production of hydroxybutyrate and subsequently acetoacetate. In panic mode, there is also an excess production of stress hormones that antagonize the already deficient action of insulin --- a perfect example of a pathological positive feedback loop vicious cycle. Free fatty acids are mobilized to give the liver plenty of substrate to produce ketones as a source of energy. (The free fatty acid levels are much less than the ketone levels, and contribute nil to the ketoacidosis.)

The beta-hydroxybutyrate and acetoacetate are fully dissociated in blood fluids, which leaves excess hydrogen ions (acid), with two results. The extreme levels of acid tax the buffering system in the blood, particularly and immediately

depleting the bicarbonate system. The second effect of the excess acetoacetate is that it can only be eliminated via the kidneys along with a cation (usually Na+ or K+). With the excretory mechanism dominated by the acetoacetate, the kidneys cannot eliminate chloride, and so it is reabsorbed. This Hyperchloremic Acidosis is the true cause of the acidity in a diabetic ketoacidosis. In other words, it is not the presence of beta-hydroxybutyrate, and not even the presence of acetoacetate, nor even the tying up of all the alkaline buffers, but the hyperchloremic state that is the culprit.

----- In contrast ----- the ketoalkalosis caused by fasting, or by a Ketogenic Imbalance, has nothing to do with chloride retention, nor an overwhelming of the blood buffers with beta-hydroxybutyrate or acetoacetate, but rather is associated with the Henderson-Hasselbalch equation. --- In very over-simplified terms --- H+ = (CO2 + H2CO3) / HCO3-. --- In other words, acidity is proportional to carbon dioxide (plus carbonic acid), and inversely proportional to bicarbonate.

What happens in patients who are either fasting or have a Ketogenic Imbalance is a deficiency of the ability to produce carbon dioxide via the Citric Acid Cycle. In other words, a greater percentage of energy is produced by metabolizing fats via the beta-hydroxybutyrate pathway as opposed to the Citric Acid Cycle. --- So --- there is less (CO2 + carbonic acid) in relation to the amount of bicarbonate in the body. It is this ratio (not the absolute quantities of the substrates) that determines the body pH. In these cases of low (carbon dioxide + carbonic acid), you will have a tendency to elevated saliva pH, a slow respiratory rate, and increased breath holding time.

This concept of a ketoalkalosis finally coalesced into a clear picture for me years ago when I read a study in the March 1989 American Journal of Physiology. The particular reference is:

LaGrange, et al. Ketoacid production in acute respiratory and metabolic acidosis and alkalosis in rats.

----- For more than a decade I had wrestled with this concept of a ketoalkalosis without finding it written up anywhere in the literature. I had come to the conclusion that either I was totally crazy, or the entire medical ketoacidosis paradigm was completely off base. I kept finding patient after patient who slipped further into an Alkalosis when either fasting, or on a low carbohydrate diet, or when over-treated for an Acidosis, or who had thyroid insufficiency

(with associated deficient CO2 production). --- And the more ketones the person produced in the urine, the more Alkaline was the Imbalance.

Finally, the work of LaGrange substantiated my observations, and explained them fully. LaGrange found that Metabolic Acidosis inhibits and Metabolic Alkalosis enhances ketoacid production in both humans and animals. LaGrange found that in the presence of ketosis, he could inject hydrochloric acid and immediately end the ketosis. LaGrange found that ketones could actually be produced by intravenous infusions of sodium bicarbonate. LaGrange found that the ketosis associated with Alkalosis applied to not only a Metabolic Alkalosis but a Respiratory Alkalosis (hypocapnia/hyperventilation) as well. Furthermore, LaGrange found that most diabetics --- those who are not in a crisis situation --- even Type I Insulin Dependent Diabetics --- spend most of their time in a ketoalkalosis, not a ketoacidosis.

What about the ketones in the urine of a Dysaerobic patient? This is a special case. In a Dysaerobic patient, we are not dealing with the insufficient carbon dioxide production of a ketoalkalosis, nor with the overwhelming load of acetoacetate in a diabetic --- but rather with uncontrolled free fatty acid catabolism associated with oxidative free radical damage. Dysaerobic patients will tend to be alkaline at the tissue level, and thus experience alkaline pain and other symptoms of an alkaline nature (such as vertigo and itching), and yet will be acid at the systemic level. The only way to reverse the tendency to ketosis in a Dysaerobic patient is with proper supplementation with Oxy D and Oxy D+, along with a high sterol fat and low polyunsaturated fatty acid diet.

Production of ketones (especially B-hydroxybuterate) = decreased renal uric acid excretion and increased [uric acid] (= DYS and KETO Imbalance)

- due to a change in the NAD/NADH ratio
- Alcohol consumption = increases [lactic acid], which has the same effect on [uric acid]
- Most gout patients are obese, 52% have Type IV hyperlipidemia, and 36% have hypertension --- But --- hyperuremics without gout do not show hypertension of hyperlipidemia

- RNA consumption = increased [uric acid] and increased uric acid secretion

- Thiazide Diuretics = decreased uric acid excretion = precipitate gout attacks

- High SpGr = Nitrogen eliminated as uric acid = causes low UpH
  Low SpGr = Nitrogen eliminated as ammonia = causes high UpH
  Normal SpGr = Nitrogen eliminated as urea
  Water Restriction = increased purine catabolism = increases urine uric acid = low UpH

- Fructose consumption = Fruit, Honey, Sucrose (= 50% Fructose):

  - increases [lactic acid], decreases [phosphate], decreases [glucose] resulting from phosphorylation of fructose into fructose-1-P and its entrance into the glycolytic pathway

  - = also, increases [uric acid] by stimulating the increased degradation of purine nucleotides

  - = also, decreases concentration of ATP and inorganic P within the cell = which stimulates the breakdown of AMP into inosine --- then, to uric acid

ADDENDUM ON KETOACIDOSIS:

KETOACIDOSIS is a high anion gap Metabolic Acidosis due to excessive blood concentration of ketone bodies 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 always present.

- An associated Lactic Acidosis may mask the presence of the ketoacidosis because the Lactic Acidosis decreases the acetoacetate to beta-hydroxybutyrate ratio since NAD+ is produced in the production of lactate.

- The 3 major types of ketosis relevant to medical physicians are:

  - Starvation Ketosis:

a. The starvation acidosis, even with prolonged fasting, is only mild to moderately severe, with keto anion levels up to a maximum of 3-5 mmol/l and plasma pH down to 7.3. This lack of severity is probably due to the insulin level, which though lower, is still enough to keep the FFA level < 1 mM. The limit of FFA availability as a substrate to the liver restrains hepatic ketogenesis. Also, ketone bodies stimulate some insulin release from the pancreas.

- Alcoholic Ketoacidosis:

  a. Insufficient food intake decreases glycogen stores, decreases insulin, and increases glucagon. Hepatic metabolism of ethanol to aldehyde and then to acetate both involve NAD+ as a cofactor.

     i. The NADH/NAD+ ratio rises, and this both inhibits gluconeogenesis and favors the production of beta-hydroxybutyrate over acetoacetate. The insulin deficiency results in increased mobilization of FFA from adipose tissue. The decreased insulin/glucagon ratio results in a switch in hepatic metabolism favoring increased beta oxidation of fatty acids. The beta oxidation of fatty acids results in an increased production of acetyl-CoA, which forms acetoacetate.

     ii. Acidemia may be severe.

     iii. Plasma glucose may be depressed or normal or even elevated.

     iv. Magnesium deficiency is not uncommon.

     v. A mixed disorder may be present with a Metabolic Alkalosis (due to vomiting), or a Respiratory Alkalosis.

- Diabetic Ketoacidosis:

  a. An absolute or relative lack of insulin leads to diabetic metabolic compensation. There may be a precipitating factor such as infection or stress causing an excess of stress hormones that antagonize the actions of insulin.

b. FFA mobilization is initiated by the effect of absolute or relative insulin deficiency on fat cells. FFA levels can be quite high, providing the liver with plenty of substrate to produce ketones. (The FFA levels are much less than ketone levels, and contribute only a small amount to the Metabolic Acidosis.)

c. The major switch in hepatic lipid metabolism occurs in response not just to insulin deficiency, but also to the concomitant rise in levels of the stress hormones glucagon, corticosteroids, catecholamines, and growth hormone.

   i. The hepatic effects of a fall in the insulin/glucagon ratio are increased glycogenolysis, increased gluconeogenesis, and increased ketogenesis.

d. Why does the major switch in hepatic metabolism occur?

   i. The inhibition of the enzyme acetyl-CoA carboxylates is probably the key step. This enzyme is inhibited by increased FFA levels, decreased insulin levels, and particularly by the rise in glucagon. All 3 of these factors are present in DKA.

Acetoacetic acid and beta-hydroxybutyric acid dissociate, producing H+, which is buffered by HCO3- in the blood. For each anion produced there is a loss of 1 bicarbonate. The increase in the anion gap (representing the increase in the unmeasured acid anions) should approximately equal the decrease in the [HCO3-].

- In some cases, a <u>Hyperchloremic</u> Metabolic Acidosis develops.

  - Acetoacetate and beta-hydroxybutyrate are moderately strong acids and are excreted with a cation (usually Na+ or K+) to maintain electroneutrality. The net effect is the loss of "potential bicarbonate" equaling the level of urinary ketone body loss. The HCO3- is replaced in the blood by Cl- derived from renal reabsorption. The effect is to cause a rise in plasma [Cl-] and the anion gap returns toward normal despite persistence of the Metabolic Acidosis. So, both a Ketoacidosis and a High Chloride Acidosis may be present, and the elevation of the anion gap will be

less than expected for the degree of depression in the bicarbonate level (resulting in a Δ ratio < 0.8).

- Serum potassium is commonly normal or high (due to the Acidosis) despite the presence of a large total body potassium deficit (due to renal losses).

- There is always a total body deficiency of phosphate even though blood phosphate levels may be high.

In Diabetic Ketoacidosis, the keto-acids are produced in the liver but not in every cell in the body. The intracellular alkalinizing effect of the compensatory hypocapnia (Hyperventilation = Respiratory Alkalosis) that occurs will, however, affect every cell and not just the hepatocytes.

- Does this mean that Diabetic Ketoacidosis produces an extracellular rise in [H+} but the opposite change in most tissues (excluding the liver) where the net effect is a fall in intracellular [H+] due to the compensatory hypocapnia? It should also be noted that keto-acids can enter most cells and be used as an energy substrate, and this would initially cause a fall in intracellular [H+].

- So --- a Ketoacidosis may be an appropriate term for the hepatocyte, and for the plasma that is only partially compensated, but all the other cells of the body may be suffering from a Ketoalkalosis.