Ketogenic Diets

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Ketones & Ketosis

- Ketones are organic, water soluble compounds formed from fat and some amino acids under specific circumstances i.e.
  - Fasting
  - Low carb diets
  - Starvation
  - Prolonged high intensity exercise
  - Poorly controlled Type 1 diabetes (DKA)

- The ketone bodies we produce are: acetone, acetoacetone, and beta-hydroxybutyrate (B-OHB)

- Ketosis is simply the point at which ketone production is exceeding use
Ketone Formation

Relative or absolute deficiency of insulin

Mobilization of free fatty acids from fat depots

Increased delivery of free fatty acids to the liver

Increased uptake and oxidation of free fatty acids by the liver

Accelerated production of ketone bodies by the liver

Image source:
www.nbs.csudh.edu

Image source:
dtc.uesf.edu
Ketone Formation

• The most important factor for ketone formation – glucose and insulin need to be low enough for the body to access to stored triglycerides (fat)
• If this does happen, hormone sensitive lipase (HSL) is stimulated to breakdown the triglyceride into 3 fatty acids and a glycerol (lipolysis)
• The fatty acids are taken up into the blood stream to be utilised by the tissues
Lipolysis in Adipose tissue

Hormone sensitive lipase exists in two forms inactive dephosphorylated (brought by Insulin) and active phosphorylated form (brought by glucagon, ACTH and catecholamines). Insulin promotes lipogenesis while the other hormones promote lipolysis.

Image source:
http://www.slideshare.net/namarta28/ketosis
• Once inside cells, the fatty acids are taken into the mitochondria to be metabolised via a process known as beta-oxidation
• As glucose levels become lower, beta-oxidation increases the breakdown of fatty acids and in doing so increases the production of a molecule called Acetyl-CoA
• The Acetyl-CoA is then shunted off to be used in a process known as ketogenesis
• Ketogenesis is the process where ketones are formed – initially acetoacetate then into beta-hydroxybutyrate and acetone
• The glycerol will most likely be converted to glucose via a process known as gluconeogenesis
**Ketogenesis Pathway**

**Insulin**
- inhibits lipolysis
- stim. FA synthesis

**Glucagon**
- has reverse effects
- enhances ketogenesis
- stim. Gluconeogenesis
- stim. glycogenolysis

**Triglycerides**
- Hypertriglyceridemia
- enhances ketogenesis

**Free Fatty Acids + Glycerol**

- Acetyl CoA
  - + insulin, glucose
  - + Glucose, -ketone bodies

- CO₂ + H₂O

**VLDL Triglycerides**

- Diabetes:
  - Increased
  - Hypertriglyceridemia
  - VLDL
  - Hypercholesterolemia

**Lipoprotein Lipase**
(endothelium)

- VLDL → IDL → Liver → LDL

- + insulin

- Hormone-sensitive lipase
(adipose tissue)

- + glucagon (enhances ketogenesis)

- Liver
  - (Mitochondrial Oxidation)

- Kidney, Liver

- Triglycerides or Gluconeogenesis

*Pharmacology, MUSC*

Image source: http://www.slideshare.net/dhavalshah4424/insulinandoral
Metabolic Pathway

A. Hepatic Ketogenesis
   - Acyl-CoA
   - β-Oxidation
   - Acetyl-CoA
   - mThiolase
   - AcAc-CoA
   - HMG-CoA
   - HMGCL
   - AcAc
   - βOHB
   - Acetone

B. Ketone Body Oxidation
   - βOHB
   - NAD+
   - BDH1
   - NADH
   - Succinyl-CoA
   - Succinate
   - SCOT
   - AcAc
   - Succinate
   - Fatty acids
   - Acetyl-CoA
   - TCA Cycle

C. Non-Oxidative Fates of Ketone Bodies
   - AcAc
   - AACS
   - AcAc-CoA
   - Succinate
   - cThiolase
   - Acetate
   - HMG-CoA
   - HMGCS1
   - Mevalonate
   - Cholesterol Synthesis
   - ACC
   - HCO3
   - ATP
   - PDH
   - Pyruvate
   - Malonyl-CoA
   - DNL

Image source: ajpheart.physiology.org
What level of Ketosis is optimal?

- Optimal Fuel Flow for Brain and Muscles
- Optimal Ketone Zone
- Nutritional Ketosis Begins
- Post-Exercise Ketosis
- Starvation Ketosis
- Ketoacidosis

Blood Ketones (millimolar): 0 to 5.0

Page 91: The Art and Science of Low Carbohydrate Performance
Jeff S. Volek and Stephen D. Phinney
Keto Myths

Ketosis is dangerous

- Dietary ketosis vs diabetic ketoacidosis
- Dietary ketosis is not dangerous and is actually a very favourable metabolic environment
- Diabetic ketoacidosis is where ketone levels become very high and can shift the blood pH into dangerously acidic levels
- Because of the presence of insulin, it is unlikely for a T2D to experience ketoacidosis but a T1D could do this by simply stopping insulin injections
- Diabetic ketoacidosis is a life-threatening medical emergency
Keto Myths

Carbs are essential

• Not so, according to the Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients) (2005):
  • “The lower limit of dietary carbohydrate compatible with life apparently is zero, provided that adequate amounts of protein and fat are consumed. However, the amount of dietary carbohydrate that provides for optimal health in humans is unknown. There are traditional populations that ingested a high fat, high protein diet containing only a minimal amount of carbohydrate for extended periods of time (Masai), and in some cases for lifetime after infancy (Alaska and Greenland Natives, Inuit, and Pampas indigenous people)(DuBois, 1928; Heinbecker, 1928). There was no apparent effect on health or longevity.” (Food and Nutrition Board; Institute of Medicine,p.275,2005)
• There is no such thing as an essential carbohydrate, unlike with fatty acids and amino acids
• Glucose is easily made via gluconeogenesis
Keto Myths

Research does not support ketogenic diets

- Most nutritional research is flawed either deliberately or accidentally (depending on your level of cynicism)
- Things that are not done properly in research
  - Keto-adaption, which takes weeks to achieve
  - Keto diets need to be under 50g of carbohydrate per day
  - The research diet does not reflect a real life keto diet
  - Focusing on red-herrings (i.e. ‘cholesterol’)

Keto Myths

You will develop a vitamin and mineral deficiency

• This is just plain old bad “science” or unfair comparison of a meat vs plant product per calorie rather than per gram
• Anyone who has done any research into vitamin and mineral composition of animal products, will realise just how healthy they are and that they are often superior to plants
• Added bonus of much lower levels of anti-nutrients that are found in plants products such as soy, grains etc.
• Extra added bonus – some vitamins are exclusively found in animal products (vitamin B12, vitamin K2)
• Vitamin K2 (very different to K1) is amazing and has been found to prevent calcification of arteries (thereby lowering CVD risk). K2 is found in animal products and fermented foods
Keto Myth

You’ll give yourself a heart attack

- Puhlease?! Get over saturated fat
- A meta-analysis conducted by Siri-Tarino et. al. (2010) concluded, after analysing over 300,000 subject’s data, that there was no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD.
- The concept of “cholesterol” is completely unscientific and needs urgent re-assessment
- LDL-p is a greater indicator of heart disease risk and it is elevated via a high processed carbohydrate diet (Wood et. al., 2006)
Therapeutic Application

• “Very-low-carbohydrate diets or ketogenic diets have been in use since the 1920s as a therapy for epilepsy and can, in some cases, completely remove the need for medication. From the 1960s onwards they have become widely known as one of the most common methods for obesity treatment. Recent work over the last decade or so has provided evidence of the therapeutic potential of ketogenic diets in many pathological conditions, such as diabetes, polycystic ovary syndrome, acne, neurological diseases, cancer and the amelioration of respiratory and cardiovascular disease risk factors. The possibility that modifying food intake can be useful for reducing or eliminating pharmaceutical methods of treatment, which are often lifelong with significant side effects, calls for serious investigation.” (Paoli et. al., 2013)
Therapeutic Application

• Alzheimer’s
  ▫ Classified by some as type 3 diabetes
  ▫ Some studies have implicated high saturated fat intake in the pathogenesis of Alzheimer's but these studies did not consider the carbohydrate intake nor consider the ketogenic diet
  ▫ There are a number of theories that ketogenic diets offer protection against Alzheimer's and can be used as a complementary treatment strategy (Gasior, Rogawski & Hartman, 2006)

• Diabetes
  - The most simple definition for diabetes is an intolerance to carbohydrate
  - This is simply because (for whichever underlying reason) the body is unable to utilise the metabolised form of carbohydrate, glucose
  - The removal of carbohydrate requires the replacement with another macronutrient i.e. fat
Therapeutic Application

• Epilepsy
  ▫ “The ketogenic diet has been in clinical use for over 80 years, primarily for the symptomatic treatment of epilepsy. A recent clinical study has raised the possibility that exposure to the ketogenic diet may confer long-lasting therapeutic benefits for patients with epilepsy. Moreover, there is evidence from uncontrolled clinical trials and studies in animal models that the ketogenic diet can provide symptomatic and disease-modifying activity in a broad range of neurodegenerative disorders including Alzheimer’s disease and Parkinson’s disease, and may also be protective in traumatic brain injury and stroke.” (Gasior, Rogawski & Hartman, 2006)
Therapeutic Application

• Cancer
  ▫ Has a preference for utilising anaerobic glycolysis for ATP requirements (i.e. glucose driven)
  ▫ Most cancers require glucose and lack metabolic flexibility
  ▫ Ketogenic diets are showing to be antiangiogenic, anti-inflammatory and pro-apoptotic (Seyfried et. al., 2008)
  ▫ Ketogenic diets may also assist via a reduction in insulin and IGF-1 (growth factors)
  ▫ More potent as a preventative than a cure
Therapeutic Application

- Depression and bipolar
  - Psychiatrist Rif El-Mallakh believes people confuse low energy with depression or sugar crashes with mood swings
  - He says most people do better with dietary interventions alone
  - Some of his clients with bipolar found relief with the ketogenic diet
  - From “Ketogenic diet fights depression, bipolar disorder and aids weight loss” ([Examiner.com](http://www.Examiner.com))
Weight Loss

• In research, low carb diets almost always do better for weight loss than low fat
  ▫ “Severely obese subjects with a high prevalence of diabetes or the metabolic syndrome lost more weight during six months on a carbohydrate-restricted diet than on a calorie- and fat-restricted diet, with a relative improvement in insulin sensitivity and triglyceride levels, even after adjustment for the amount of weight lost.” (Samaha et. al., 2003)
  ▫ The low carbohydrate diet appears to be an effective method for short-term weight loss in overweight adolescents and does not harm the lipid profile (Sondike et.al., 2000)
• Low carb combined with high fat promotes powerful appetite hormones
• You tend to eat less and have more energy
• The ketogenic diet/LCHF diet is only effective if you stick to it
• It is easier to stick to as fat is delicious so you don’t feel deprived once you move past your carb addiction
Athletes

“Compared to highly trained ultra-endurance athletes consuming an HC diet, long-term keto-adaptation results in extraordinarily high rates of fat oxidation, whereas muscle glycogen utilization and repletion patterns during and after a 3 hour run are similar.” (Volek et. al., 2015)

- Movie – “Running of Fat”
- Clinical Sports Nutrition (Burke & Deakin) acknowledges fat adaption and that in the studies they undertook, performance was generally not impaired via high fat diets
- These researchers have set their reputation upon their findings therefore the high carb, low fat dogma remains
Fat Adaption in Well-Trained Athletes: Effects on Cell Metabolism

• “The performance of prolonged (>90 min), continuous, endurance exercise is limited by endogenous carbohydrate (CHO) stores.”
• “For many decades, sports nutritionists and exercise physiologists have proposed a number of diet-training strategies that have the potential to increase fatty acid availability and rates of lipid oxidation and thereby attenuate the rate of glycogen utilization during exercise.”
• One such strategy is "fat adaptation", an intervention in which well-trained endurance athletes consume a high-fat, low-CHO diet for up to 2 weeks while undertaking their normal training and then immediately follow this by CHO restoration (consuming a high-CHO diet and tapering for 1-3 days before a major endurance event)
• Compared with an isoenergetic CHO diet for the same intervention period, this "dietary periodization" protocol increases the rate of whole-body and muscle fat oxidation while attenuating the rate of muscle glycogenolysis during submaximal exercise. Of note is that these metabolic perturbations favouring the oxidation of fat persist even in the face of restored endogenous CHO stores and increased exogenous CHO availability (Burke et.al., 2011)
“Fat adaptation” for athletic performance: The nail in the coffin?

- ENDURANCE ATHLETES have a high capacity for the oxidation of fat during exercise .....this capacity can be easily upregulated by the chronic consumption of a low-carbohydrate (<2.5 g·kg\(^{-1}\)·day\(^{-1}\)), high-fat (\(~65–70\%\) of energy) diet. For example, 2–4 wk of exposure to such a diet in trained individuals has been shown to markedly increase fat oxidation and reduce the utilization of muscle glycogen during subsequent submaximal exercise (\(10, 11\)).

- The research goes on to describe the glycogen sparing effect as “glycogen impairment” (based on one study) and that this is the “nail in the coffin” (Burke & Kiens, 2006)

- Most of the studies on low carb high fat, are done for very short periods of time and periodised between high fat and high carb

- The research (as indicated above) does not meet a typical low carb diet as it is based on <2.5g/kg/day

- For an 80kg man this would equate to <200g of carbohydrate which is hardly low carb
Keto for Everyone?

- Keto is not everyone
- Some medical conditions are contraindicated by this diet
- If you’re pregnant, a more moderate carbohydrate intake is advised
- Some people can not keto/fat adapt
- Some people hate it
- Some people get the results they need without it
- Nutrition is individual!!
How to Keto?

Carbs
- The focus is on keeping carbohydrate to less than 50g per day
- Focus on carbohydrate (veg) that will not elevate blood glucose levels (check this yourself)
- Very little fruit (berries occasionally)
- Some veg needs to be restricted (starchy/sweet veg)
- No sugar
- No grains etc.
- Limit all processed carbohydrate
How to Keto?

Protein
• Keep your protein intake moderate (i.e. 1.0 -1.6 g/kg/day
• Meat, fish, poultry, seafood, eggs, nuts, organ meat ✓✓✓
• Limit all processed meat

Fat
• Enjoy saturated fat liberally
  ▫ Cheese, cream, plain yogurt, coconut oil, coconut cream, coconut milk, ghee, lard (more of a monounsaturated fat)
• Steer clear of polyunsaturated fats (seed oils, margarine, vegetable oils etc.)
• Enjoy some monounsaturated fats (avocado, olive oil)
• Limit all processed fat
How to Keto?

- Be liberal with your fat
- If in doubt, drop your carbs and bump up your fat
- Take sodium tablets
  - Insulin has an ability to prevent the kidneys from excreting sodium
  - As you go through ketosis, the kidneys start dropping sodium due to lowered insulin levels (this is why ketosis has a diuretic effect)
  - If you’re feeling terrible (i.e. carb flu) take some sodium tablets (2-5g per day)
  - Don’t stress about sodium – study published in the New England Journal of Medicine (2014) concluded that the optimal sodium intake is between 4-6grams per day and that when you cut back to the recommended intake of 2.3g/day (AHA) you increase your risk for CVD and all-cause mortality by 50%. (O’Donnell et. al., 2014)
How Do I Know I’m in Ketosis?

- Buy a ketoanalyser
- Urine strips are not very accurate
- If you’re very thirsty and urinating a lot, it’s likely you’re in ketosis
- Breath might smell strange
- Carb flu
My Business

• Located in Ipswich, QLD
• EP Clinic - focusing on the treatment of chronic disease via nutrition and exercise
• Group fitness classes
• Diabetic group fitness classes
• Online 8 Week Challenge focusing on education, health and fitness

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