THE FAT ON KETOSIS AND THE KETOGENIC DIET

The high-fat, low-carb ketogenic diet remains a contentious issue, but research has indicated a plethora of benefits beyond the diet industry's claims of fat burning, says exercise physiologist *Tony Boutagy*.

A sure way to start a bar brawl during drinks at any medical or nutritional conference is to ask fellow delegates and presenters what they think about a ketogenic diet. Similarly, if you would like to lose three days of your life, just search the internet forums on ketosis and down the rabbit hole you'll go.

It is ironic that in this day and age, when we know more about the effects of ketones on health, cognition and performance than any other time in history, the term 'ketone' and it's family members 'ketogenic diet', 'ketosis' and 'supplemental ketones' have the ability to invoke such hostility and derision among medical and nutritional professionals.

Recently I was enjoying dinner with a leading medical professional. The conversation turned to the treatment of epilepsy and I suggested there was a place for the use of a ketogenic diet. I was advised, in no uncertain terms, to 'not go there'.

There are several reasons for this prevalent attitude but, most likely, chief amongst them is that the ketogenic diet advises that 80 to 90% of energy needs be consumed in the form of fat.

However, we can say with a great degree of certitude that a reason why most people feel a little uncomfortable when the discussion turns to ketosis is *not* because of an absence of research in the field.

Keto basics

Let's take a step back and define some terms and look at the history of the ketogenic diet.

Ordinarily, human bodies run on a mixture of carbohydrate and fats. Each meal we consume props up our blood sugar level, and we primarily run on carbohydrates. When our blood glucose levels begin to drop,

we generally eat our next meal. While we sleep at night, our bodies shift to running on a higher amount of fat for metabolism and for the physical repair that occurs during our sleep cycles, but glucose is still primarily used to support our active brains during dreaming.

However, if we consume a diet that removes a considerable portion of carbohydrates and replaces them with fat, within 24 hours or so, our liver and muscles become depleted of their carbohydrate stores and our body mobilises body fat, transporting it to the liver, which produces an 'alternative fuel source' known as ketone bodies.

Ketone bodies, which are technically water-soluble chemical substances, are comprised of acetoacetate, beta-hydroxybutyrate and acetone. Once released by the liver, ketones enter into the blood stream and all cells with mitochondria can take ketone bodies up from the blood and reconvert them into acetyl-CoA, which can then be used as fuel in their citric acid cycles. Unlike free fatty acids, ketone bodies can cross the blood-brain barrier (a semipermeable membrane that can impede the passage of cells, particles, and large molecules) and are therefore available as fuel for the cells of the central nervous system, acting as a substitute for glucose, on which these cells normally survive.

Elevated levels of ketones in the blood can occur via several methods, namely during starvation, fasting, prolonged heavy endurance exercise, consuming supplemental ketone salts or esters or by eating a low carbohydrate, high fat ketogenic diet.

The term 'ketone bodies' was first coined in 1921 by Rollin Woodyatt and the ketogenic diet was used by Rollin Woodyatt at the Mayo Clinic in the treatment of paediatric epilepsy later that year[1]. Its success in this area saw widespread use for over a decade until the introduction of anticonvulsant drugs. However, in those cases where medication did not control seizures, the ketogenic diet was again used with a high degree of effectiveness[2].

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It is interesting to note that the ancient Greeks, around 400 BCE, used fasting as a treatment for epilepsy. Our modern understanding of how fasting induces rapid production of ketone bodies sheds light on why the Greeks were able to achieve success when treating this illness – a state of ketosis helps control seizures due to it's effectiveness in achieving brain energy homeostasis[3] (Hippocrates, *On the Sacred Disease*).

Continuing in the tradition of the Greeks, the world leaders in researching and treating paediatric epilepsy is Johns Hopkins University in America[4]. 90 years of research has demonstrated that nutritional ketosis is important for the metabolic management of many diseases, but especially seizures. Nutritional ketosis works similarly to fasting: during the abstinence from food, humans liberate free fatty acids from the adipose tissue and break down stored glycogen levels in the liver. Once the glycogen levels reach a threshold low level, we start accelerating the oxidation of fatty acids in the liver.

The heart and muscles prefer fatty acids over glucose, but fatty acids do not

readily cross the blood-brain barrier. So brain energy metabolism will transition from glucose to ketone bodies within a few days of fasting or a ketogenic diet. These ketone bodies represent water-soluble fat molecules that readily cross the blood-brain barrier and help preserve, maintain and enhance brain energy metabolism in the face of starvation.

The late George Cahill performed pioneering research in the 1950's, laying the foundation for our current understanding of fasting physiology[5]. The ketogenic diet has a macronutrient ratio that mimics the physiological state of fasting: high fat, moderate protein, and very low carbohydrate – essentially, 5% of energy needs coming from carbohydrate, 10-30% from protein and the remainder (around 80%) from fat.

Recent research

Research on ketones and ketosis is now far reaching, with studies exploring the diet or supplemental ketones for seizure control, cancer (in particular, brain and metastatic cancer), traumatic brain injury, neurodegenerative diseases, dementia, Alzheimer's disease, Parkinson's disease, stroke, ALS, and muscle wasting. Exciting new research has been examining the effect of ketones on the mitigation of CNS oxygen toxicity that is common in Navy divers, testing the preservation of cognitive resilience and physical functions under conditions of hypoxia, in the protection against cellular, tissue and physiology damage in people exposed to radiation both in space for astronauts and in cancer treatments[6]. Adrienne Scheck at the Barrow Neurological Institute has performed animal studies on glioblastoma (brain tumour) showing that if animals are in a state of nutritional ketosis, the tumours are sensitised to radiation, thus making the radiation much more lethal to the cancer, because ketones have an anti-cancer effect. Scheck's research has indicated that a ketogenic diet could make the immune system hyper-vigilant in seeking out cancer cells[7].

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Several research groups are examining cancer metabolism in response to states of ketosis. Cancer growth is tightly linked to insulin levels and the liver's production of ketones is regulated by decreased insulin. A ketogenic diet abolishes post-meal spikes in glucose and insulin, which would go towards explaining the efficacy of ketosis as a metabolic therapy for both cancer and seizure management.

Research performed over the last decade has allowed ketones to be appreciated as an efficient metabolic substrate for cells and a powerful signalling molecule that can increase brain-derived neurotropic factor (BDNF), and influence inflammation and endogenous antioxidant status in cells[8] which can have a direct positive impact on several processes involved in ageing[9], promoting longevity[10] and improved cognition with advancing years[11].

The 30-second article

- The ketogenic diet advises that 80 to 90% of energy needs be consumed in the form of fat
- This forces the body to use body fat as the energy source rather than carbohydrates, which prompts a transition from glucose metabolism to an 'alternative fuel source' known as ketone bodies
- The keto diet is still divisive in medical and nutritional circles, although 90 years of research has demonstrated that nutritional ketosis can play a role in the metabolic management of diseases including epilepsy, cancer, Alzheimer's disease and Parkinson's disease
- Research has generally shown that once adapted to the ketogenic diet, strength performance, body composition and endurance performance do not seem to be impaired
- Studies have found that those on a ketogenic diet reported less hunger and experienced a 50% reduction in insulin levels, which has implications for those who have difficulty controlling appetite and those with elevated insulin levels.

Adapting to switching fuels

If we swap the majority of the carbohydrate in our diet for fat, **how quickly do we switch from glucose burning to fat-metabolism?** The answer varies from person to person, as there are considerable individual differences in the degree of metabolic flexibility that allow us to switch metabolic substrates effortlessly. Most studies show that the transition from glucose metabolism to ketosis, where beta-hydroxybutyrate levels are consistently over 0.7 mmol/l, occurs within around 5 days. Leading expert in the field, professor Dominic D'Agostino, has suggested that the length of time it takes for the metabolic machinery (enzymes, transporters and mitochondria) to adapt to ketone metabolism might be anywhere from 2 weeks to 8 months, with the average being 3 to 6 months. This means one would experience a short-term reduction in physical performance until the metabolism had fully adjusted to the alternative fuel source.

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Research has generally shown that once adapted to the ketogenic diet, strength performance12, body composition13 and endurance performance14 do not seem to be impaired. However, a recent study by Professor Louise Burke and colleagues found that a 3-week ketogenic diet in elite level race walkers reduced efficiency and performance15. An issue worth noting when interpreting these findings is that the period of time that the athletes were given to adjust from habitually consuming a very high carbohydrate diet was only three weeks. Considering D'Agostino's theory of several-month adaptation mentioned above, it remains to be determined if different results might have been seen if the diet was continued over several months.

Who can keto?

Ketogenic diets are not suitable for everyone. Professor D'Agostino has stated that roughly 20% of the population might have issues handling such a high-fat diet, due to genetics, reasons related to the microbiome, or fatty acid oxidation disorders. It would be advisable to have several blood tests within a few months of transitioning to the ketogenic diet in order to assess lipid status and ensure no adverse responses to the high fat content.

Individuals who tolerate carbohydrate-rich diets well (hunger is controlled, few post-meal dips in energy, no blood sugar crashes) would most likely find little benefit from swapping to a ketogenic diet, as they are already insulin sensitive. Conversely, it is now well accepted that those with type II diabetes and insulin resistance, which is typified by carbohydrate intolerance, would most benefit from adopting a low carbohydrate, high fat diet[16].

Fat burning?

Many people are attracted to the ketogenic diet because of the surface claim that you will increase 'fat burning'. Despite the clear metabolic shift from glucose metabolism to fat during ketosis, research has clearly demonstrated that the primary driver of weight loss is a negative energy balance over time and not the diet type. This was recently shown in two very well controlled studies led by Dr Kevin Hall at the NIH[17]. Hall did note that most subjects on the ketogenic diet reported less hunger and had difficulty eating all the food amounts they needed to for the study, and all subject's insulin levels were reduced by 50%. This has enormous implications for those who have difficulty controlling their appetite, overeating and those with elevated insulin levels.

Throughout the evolution of humans, we have developed an ability to be metabolically flexible, that is, able to switch from glucose metabolism to fat-based fuels depending on food (carbohydrate) availability. When we transition to a diet that produces ketones, there is a significant reduction in 24-hour insulin levels, post-meal fluctuations in glucose/insulin and overall reduction in systemic inflammation, which makes the diet attractive and worthy of consideration by those with insulin resistance, type II diabetes, neurodegenerative disease (and those at risk and those with a family history), epilepsy, certain cancers and anyone interested in ageing well with cognitive resilience and ability. **N**

Tony Boutagy, PhD, AEP, ESSAM is a strength coach, exercise physiologist and the director of the Boutagy Fitness Institute in Sydney, where he both trains clients and delivers courses and mentoring programs for personal trainers. **tonyboutagy.com**

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