

Science Review: The Ketogenic Diet

Ketosis is a natural metabolic state that occurs when there is an absence or shortage of dietary carbohydrates (sources of glucose) consumed as the main energy source for the body. While in ketosis, the body shifts towards the use of fat as the primary energy source. The body increases the breakdown of fat into ketone bodies which are readily used by most tissues, including muscle and brain, as the main fuel.¹

Research Highlights

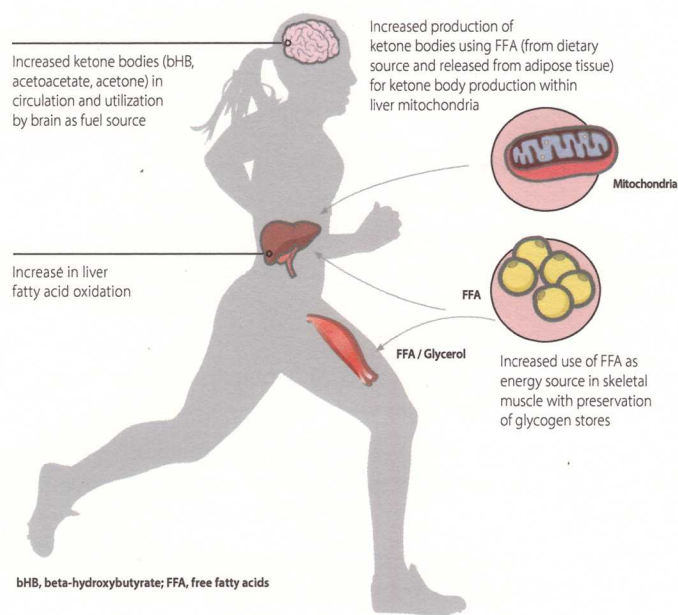
- ✓ Ketosis is a normal physiological response during which the body utilizes fat to produce ketone bodies as the main fuel for the body, including muscle and brain.
- ✓ Adapting to a ketogenic diet has been shown to have potential benefits for weight management, metabolic health, and physical and cognitive performance.
- ✓ Ketogenic approaches have evolved over the past decade to include a broader variety of components including use of medium-chain triglycerides and exogenous ketones, as well as greater understanding of clinical monitoring.

Mechanism of Action (Figure 1)

A ketogenic diet refers to a dietary approach that promotes ketosis by restricting carbohydrates (usually to < 50 g/day) and increasing the intake of fat with adequate (low to moderate) consumption of protein. The following metabolic adaptations (keto-adaptation) occur as a result of adopting a ketogenic diet:¹

- Glucose levels decrease and so does the need for insulin (to regulate glucose).
- A reduction in circulating insulin levels helps reduce lipogenesis (fat accumulation) and increases lipolysis, resulting in increased levels of free fatty acids (FFA) for utilization as a source of energy.
- The body (mainly the liver) increases fatty acid oxidation to generate ketone bodies [i.e., acetoacetate, β -hydroxybutyrate (bHB), and acetone] in order to meet the energy demands.
- Ketone bodies in circulation provide a stable source of fuel for the body and the brain, thereby sparing the need to convert protein into glucose as energy supply.

Figure 1. How Ketosis Works in the Body



Weight Management

Systematic reviews² of clinical studies have demonstrated the potential effectiveness of ketogenic diets in weight management:

- Ketone bodies generated while in a state of ketosis may have effects on appetite-controlling hormones (e.g., ghrelin and leptin) or may have direct appetite-suppressing properties.^{3,4}
- The reduction in fat accumulation and increase in fat oxidation during ketosis help promote fat loss.^{5,6}
- Individuals on a ketogenic diet are less hungry and have a reduced desire to eat.^{7,8}

Cardiovascular and Blood Glucose Management

Adapting to a ketogenic diet has been shown to lead to several metabolic advantages and may be beneficial for diabetes management and cardiovascular disease risk reduction.^{9,10}

- Improvements in glycemic control (especially in individuals with type 2 diabetes): with restricted carbohydrate consumption, hepatic glucose output is reduced and the circulating levels of glucose are more efficiently controlled. Subsequently, the need for insulin decreases, and insulin sensitivity is improved.¹¹

- Improvements in blood lipids: increased fatty acid oxidation leads to lower serum triglycerides levels. Lower insulin levels inhibit HMG-CoA reductase leading to a decrease in endogenous cholesterol synthesis and cholesterol levels. Ketogenic diets have also been associated with increases in HDL-cholesterol and the size and volume of LDL-cholesterol particles.^{1,12}
- Anti-inflammatory properties: High intakes of carbohydrates have been linked to low-grade inflammation, whereas diets high in unsaturated fat are associated with decreased inflammation.^{13,14} Ketogenic diets have been shown to elevate blood anti-oxidative capacity¹⁵ and have been found to decrease reactive oxygen species (ROS) in mitochondria.¹⁶

Athletic Performance

Emerging evidence suggests that ketogenic diets may be beneficial for athletic performance:

- In the keto-adapted state, the human body utilizes fatty acids and ketone bodies as the primary fuel for exercise, thus minimizing the breakdown of lean muscle tissue.¹
- The ability to maintain lean body mass while burning fat is beneficial for body composition and the power-to-weight ratio.⁵
- Ketosis is associated with a reduction in the generation of ROS by mitochondria and, therefore, potentially leads to less tissue damage and faster recovery.⁵
- With the ability to use fat as fuel, the brain has a steady supply of ketone bodies during prolonged exercise, bypassing the need for high carbohydrate intakes and sustaining physical and cognitive performances.⁵

References:

1. Paoli A, et al. *Eur J Clin Nutr.* 2013;67(8):789-96.
2. Bueno NB, et al. *Br J Nutr.* 2013;110(7):1178-87.
3. Sumithran P, et al. *Eur J Clin Nutr.* 2013;67(7):759-64.
4. Johnstone AM, et al. *Am J Clin Nutr.* 2008;87(1):44-55.
5. Volek JS, et al. *Eur J Sport Sci.* 2015;15(1):13-20.
6. Volek JS, et al. *Metabolism.* 2002;51(7):864-70.
7. Gibson AA, et al. *Obes Rev.* 2015;16(1):64-76.
8. McClellan FJ, et al. *Obesity (Silver Spring).* 2007;15(1):182-7.
9. Feinman RD, et al. *Nutrition.* 2015;31(1):1-13.
10. Santos FL, et al. *Obes Rev.* 2012;13(11):1048-66.
11. Boden G, et al. *Ann Intern Med.* 2005;142(6):403-11.
12. Adam-Perrot A, et al. *Obes Rev.* 2006;7(1):49-58.
13. Jonasson L, et al. *Annals of Medicine.* 2014;46(3):182-7.
14. Schulze MB, et al. *Am J Clin Nutr.* 2005;82(3):675-84; quiz 714-5.
15. Nazarewicz RR, et al. *Rejuvenation Res.* 2007;10(4):435-40.
16. Maalouf M, et al. *Neuroscience.* 2007;145(1):56-64.
17. Paleologou E, et al. *J Clin Med.* 2017;6(6).
18. Gano LB, et al. *J Lipid Res.* 2014;55(11):2211-28.
19. Bough KJ, et al. *Epilepsia.* 2007;48(1):43-58.
20. Sullivan PG, et al. *Ann Neurol.* 2004;55(4):576-80.
21. Newnman JC, et al. *Trends Endocrinol Metab.* 2014;25(1):42-52.
22. Lutas A, et al. *Trends Neurosci.* 2013;36(1):32-40.
23. Crane PK, et al. *N Engl J Med.* 2013;369(6):540-8.
24. Ojo O, et al. *Int J Environ Res Public Health.* 2015;12(7):8281-94.
25. Cunnane SC, et al. *Ann NY Acad Sci.* 2016;1367(1):12-20.
26. Goday A, et al. *Nutr Diabetes.* 2016;6(9):e230.
27. McAuley KA, et al. *Diabetologia.* 2005;48(1):8-16.
28. Johnston CS, et al. *Am J Clin Nutr.* 2006;83(5):1055-61.
29. Kossoff EH, et al. *Epilepsia.* 2009;50(2):304-17.
30. Wheless JW. *J Child Neurol.* 2001;16(9):633-5.

Neurological and Cognitive Health

Since the 1920s, ketogenic diets have been used as a therapeutic approach in the treatment of drug-resistant childhood epilepsy.¹⁷ Emerging evidence suggests that keto-adaptation may potentially be beneficial for cognitive health:

- Studies have demonstrated that ketone bodies improve mitochondrial function and metabolic efficiency by raising cerebral ATP levels while lowering the production of ROS (and subsequently oxidative stress), which have been associated with neuroprotection.^{18,19,20}
- The ketone body, bHB, may function as a signaling molecule, modulating biological and epigenetic events associated with antioxidant and anti-inflammatory properties.²¹
- Ketogenic diets have been shown to influence neurotransmitter activity and reduce neuronal excitability.²²
- Abnormal glucose metabolism in the brain, potentially caused by high carbohydrate consumption, is associated with cognitive decline, whereas a keto-adapted cerebral metabolism state bypasses the utilization of glucose.^{23,24,25}

Safety Concerns

- Some individuals on ketogenic diets may encounter tolerance issues or mild-to-moderate adverse effects such as headache, asthenia, nausea and/or vomiting, and muscle cramps.²⁶
- Some individuals on ketogenic diets may experience increases in LDL cholesterol levels, creatinine clearance, and urinary sodium and calcium excretion.^{27,28}
- Ketogenic diets are contraindicated for individuals with inborn metabolic errors in fatty acid metabolism and mitochondrial enzymes.^{29,30}

Progress Monitoring

- Before starting the diet, clinicians should evaluate medical history, analyze biochemical markers, perform physical examination, and provide a thorough consultation with individuals about strict adherence to the diet and the potential complications.
- Clinician should educate individuals on approaches to minimize gastrointestinal symptoms and ensure nutrient adequacy.
- Regular monitoring of ketone bodies (nutritional ketosis: 0.5-3.0 mM) is recommended. Monitoring can be performed with commercially available tests that determine ketone levels in urine, blood, or breath.

