EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 6
564-572
Year: 2021

TONE OF BODY IS CONTROLLED BY KETONE: THE ENORMOUS SOURCE FORM NATURE

Kushal Nandi[1]*, Dhrubo Jyoti Sen[1], Saroni Saha[1], Dhananjoy Saha[2] and Angshul Saha[3]

[1]Department of Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt Lake City, Sector–V, EM–4, Kolkata–700091, West Bengal, India.
[2]Deputy Director, Directorate of Technical Education, Bikash Bhavan, Salt Lake City, Kolkata–700091, West Bengal, India.
[3]Kendriya Vidyalaya No-1, Salt Lake, Sector-I, Labony, Kolkata-700064, West Bengal, India.

***Corresponding Author: Kushal Nandi**
Department of Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt Lake City, Sector–V, EM–4, Kolkata–700091, West Bengal, India.

Article Received on 24/04/2021 **Article Revised on 14/05/2021** **Article Accepted on 04/06/2021**

ABSTRACT
A ketogenic diet is a diet in which most of the calories come from fat (70-75%). A moderate number of calories come from protein (20-25%). Only a small number of the calories come from carbohydrates (5%). The diet forces the body to burn fats rather than carbohydrates for energy. Normally, the carbohydrates you eat are turned into glucose in the body, which is used for energy around the body and in the brain. But, if you don't eat enough carbohydrates, your body has a back-up system of burning fat instead. The liver can use stored fat and the fat you eat for energy. Stored fat is broken into two parts, fatty acids, and ketone bodies. Ketone bodies power the brain instead of glucose. This state of having a lot of ketone bodies in your blood is called "Ketosis." The liver can also make or release its own glucose through two processes (gluconeogenesis and glycogenolysis) as glucose is still needed for normal body function. The regular ketogenic diet has two to four times fatter by weight than protein, and very little carbohydrates every day. This means not eating foods that are made from starch or sugar. High-carbohydrate foods are foods like fruits, bread, pasta, grains, cookies, and ice cream. Also, you have to increase your intake of fatty foods, like oils (usually from olives, avocados, or coconuts), butter, and fatty meats. It's also important to not eat too much protein. You should only eat just enough protein so you don't lose muscles. Too much protein reduces the ketone bodies in your blood and blocks fat burning. The ketogenic diet was originally created to treat people with epilepsy. Until other medicines became available, this was a good option for managing the condition.

KEYWORDS: Medium Chain Triglyceride, Fat, Protein, Carbohydrate, Ketosis, Gluconeogenesis, Glycogenolysis.

INTRODUCTION
The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that in medicine is used mainly to treat hard-to-control (refractory) epilepsy in children. The diet forces the body to burn fats rather than carbohydrates.[1]

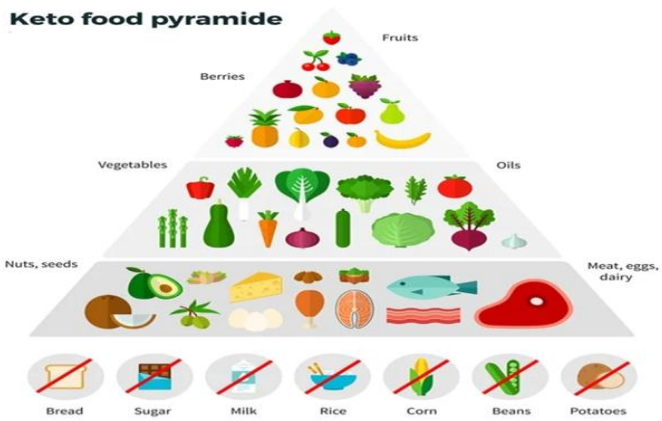

Figure 1: Keto food pyramid.

Normally carbohydrates in food are converted into glucose, which is then transported around the body and is important in fueling brain function. But if little carbohydrate remains in the diet, the liver converts fat into fatty acids and ketone bodies, the latter passing into the brain and replacing glucose as an energy source. An elevated level of ketone bodies in the blood (a state called ketosis) eventually lowers the frequency of epileptic seizures. Around half of children and young people with epilepsy who have tried some form of this diet saw the number of seizures drop by at least half, and the effect persists after discontinuing the diet. Some evidence shows that adults with epilepsy may benefit from the diet and that a less strict regimen, such as a modified Atkins diet, is similarly effective. Side effects may include constipation, high cholesterol, growth slowing, acidosis, and kidney stones.

The original therapeutic diet for pediatric epilepsy provides just enough protein for body growth and repair, and sufficient calories to maintain the correct weight for age and height. The classic therapeutic ketogenic diet was developed for treatment of pediatric epilepsy in the 1920s and was widely used into the next decade, but its popularity waned with the introduction of effective anticonvulsant medications. This classic ketogenic diet contains a 4:1 ketogenic ratio or ratio by weight of fat to combined protein and carbohydrate. This is achieved by excluding high-carbohydrate foods such as starchy fruits and vegetables, bread, pasta, grains, and sugar, while increasing the consumption of foods high in fat such as nuts, cream, and butter. Most dietary fat is made of molecules called long-chain triglycerides (LCTs). However, medium-chain triglycerides (MCTs)—made from fatty acids with shorter carbon chains than LCTs—are more ketogenic. A variant of the classic diet known as the MCT ketogenic diet uses a form of coconut oil, which is rich in MCTs, to provide around half the calories. As less overall fat is needed in this variant of the diet, a greater proportion of carbohydrate and protein can be consumed, allowing a greater variety of food choices. In 1994, Hollywood producer Jim Abrahams, whose son's severe epilepsy was effectively controlled by the diet, created the Charlie Foundation for Ketogenic Therapies to further promote diet therapy. Publicity included an appearance on NBC's *Dateline* program and ...*First Do No Harm* (1997), a made-for-television film starring Meryl Strep. The foundation sponsored a research study, the results of which—announced in 1996—marked the beginning of renewed scientific interest in the diet.

Possible therapeutic uses for the ketogenic diet have been studied for many additional neurological disorders, some of which include: Alzheimer's disease, amyotrophic lateral sclerosis, headache, neurotrauma, pain, Parkinson's disease, and sleep disorders.[2]

Table 1: Daily meal chart.

Sample meal plan for one day		
Meal	**Menu idea**	**Ingredients**
Breakfast	Egg with bacon	• 28 g egg (about half an egg) • 11 g bacon (about half a slice) • 37 g of 36% heavy whipping cream • 23 g butter • 9 g slice of apple (about 5% of one apple)
Morning snack	Peanut butter ball (serving size: 0.5 ounce)	• 6 g peanut butter • 9 g butter
Lunch	Tuna salad	• 28 g tuna fish • 30 g mayonnaise • 10 g celery • 36 g of 36% heavy whipping cream • 15 g lettuce (one large leaf)
Afternoon snack	Keto yogurt (serving size: 1.3 ounces)	• 18 g of 36% heavy whipping cream • 17 g sour cream • 4 g strawberries (about half of one small strawberry) • artificial sweetener
Dinner	Cheeseburger (no bun)	• 22 g minced (ground) beef • 10 g American cheese (half a slice of cheese) • 26 g butter • 38 g of 36% heavy whipping cream • 10 g lettuce (one medium leaf) • 11 g green beans (one spoonful)
Evening snack	Keto custard (serving size: 1.2 ounces)	• 25 g of 36% heavy whipping cream • 9 g egg (half a tablespoon) • Pure, unsweetened vanilla flavouring

Anticonvulsants and Decline: During the 1920s and 1930s, when the only anticonvulsant drugs were the sedative bromides (discovered 1857) and phenobarbital (1912), the ketogenic diet was widely used and studied. This changed in 1938 when H. Houston Merritt, Jr. and Tracy Putnam discovered phenytoin (Dilantin), and the focus of research shifted to discovering new drugs. With the introduction of sodium valproate in the 1970s, drugs were available to neurologists that were effective across a broad range of epileptic syndromes and seizure types. The use of the ketogenic diet, by this time, restricted to difficult cases such as Lennox–Gastaut syndrome, declined further.[3]

MCT diet

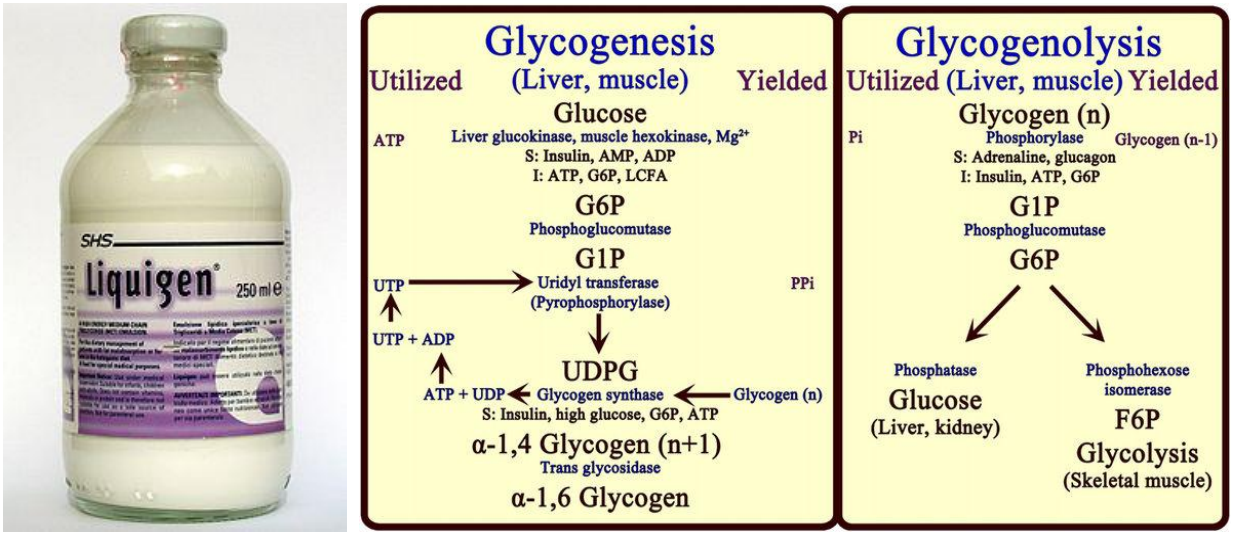

Figure 2: Medium-chain triglyceride (MCT) oil emulsion & Glycogenesis/Glycogenolysis.

In the 1960s, medium-chain triglycerides (MCTs) were found to produce more ketone bodies per unit of energy than normal dietary fats (which are mostly long-chain triglycerides). MCTs are more efficiently absorbed and are rapidly transported to the liver via the hepatic portal system rather than the lymphatic system. The severe carbohydrate restrictions of the classic ketogenic diet made it difficult for parents to produce palatable meals that their children would tolerate. In 1971, Peter Huttenlocher devised a ketogenic diet where about 60% of the calories came from the MCT oil, and this allowed more protein and up to three times as much carbohydrate as the classic ketogenic diet. The oil was mixed with at least twice its volume of skimmed milk, chilled, and sipped during the meal or incorporated into food. He tested it on 12 children and adolescents with intractable seizures. Most children improved in both seizure control and alertness, results that were similar to the classic ketogenic diet. Gastrointestinal upset was a problem, which led one patient to abandon the diet, but meals were easier to prepare and better accepted by the children. The MCT diet replaced the classic ketogenic diet in many hospitals, though some devised diets that were a combination of the two.[4]

Figure 3: Keto Diet and Inventor [Robert Atkins; 1930-2003].

Revival: The ketogenic diet achieved national media exposure in the US in October 1994, when NBC's *Dateline* television programme reported the case of Charlie Abrahams, son of Hollywood producer Jim

Abrahams. The two-year-old suffered from epilepsy that had remained uncontrolled by mainstream and alternative therapies. Abrahams discovered a reference to the ketogenic diet in an epilepsy guide for parents and brought Charlie to John M. Freeman at Johns Hopkins Hospital, which had continued to offer the therapy. Under the diet, Charlie's epilepsy was rapidly controlled and his developmental progress resumed. This inspired Abrahams to create the Charlie Foundation to promote the diet and fund research. A multicentre prospective study began in 1994, the results were presented to the American Epilepsy Society in 1996 and were published in 1998. There followed an explosion of scientific interest in the diet. In 1997, Abrahams produced a TV movie, *First Do No Harm*, starring Meryl Streep, in which a young boy's intractable epilepsy is successfully treated by the ketogenic diet.[5]

By 2007, the ketogenic diet was available from around 75 centres in 45 countries, and less restrictive variants, such as the modified Atkins diet, were in use, particularly among older children and adults. The ketogenic diet was also under investigation for the treatment of a wide variety of disorders other than epilepsy.

Efficacy: The ketogenic diet reduces seizure frequency by more than 50% in half of the patients who try it and by more than 90% in a third of patients. Three-quarters of children who respond do so within two weeks, though experts recommend a trial of at least three months before assuming it has been ineffective. Children with refractory epilepsy are more likely to benefit from the ketogenic diet than from trying another anticonvulsant drug. Adolescents and adults may also benefit from the diet, though compliance with oral diet (vs. tube fed) remains a problem.[6]

Trial design: Early studies reported high success rates; in one study in 1925, 60% of patients became seizure-free, and another 35% of patients had a 50% reduction in seizure frequency. These studies generally examined a cohort of patients recently treated by the physician (a retrospective study) and selected patients who had successfully maintained the dietary restrictions. However, these studies are difficult to compare to modern trials. One reason is that these older trials suffered from selection bias, as they excluded patients who were unable to start or maintain the diet and thereby selected from patients who would generate better results. In an attempt to control for this bias, modern study design prefers a prospective cohort (the patients in the study are chosen before therapy begins) in which the results are presented for all patients regardless of whether they started or completed the treatment (known as intent-to-treat analysis). Another difference between older and newer studies is that the type of patients treated with the ketogenic diet has changed over time. When first developed and used, the ketogenic diet was not a treatment of last resort; in contrast, the children in modern studies have already tried and failed a number of anticonvulsant drugs, so may be assumed to have more difficult-to-treat epilepsy. Early and modern studies also differ because the treatment protocol has changed. In older protocols, the diet was initiated with a prolonged fast, designed to lose 5–10% body weight, and heavily restricted the calorie intake. Concerns over child health and growth led to a relaxation of the diet's restrictions. Fluid restriction was once a feature of the diet, but this led to increased risk of constipation and kidney stones, and is no longer considered beneficial.[7]

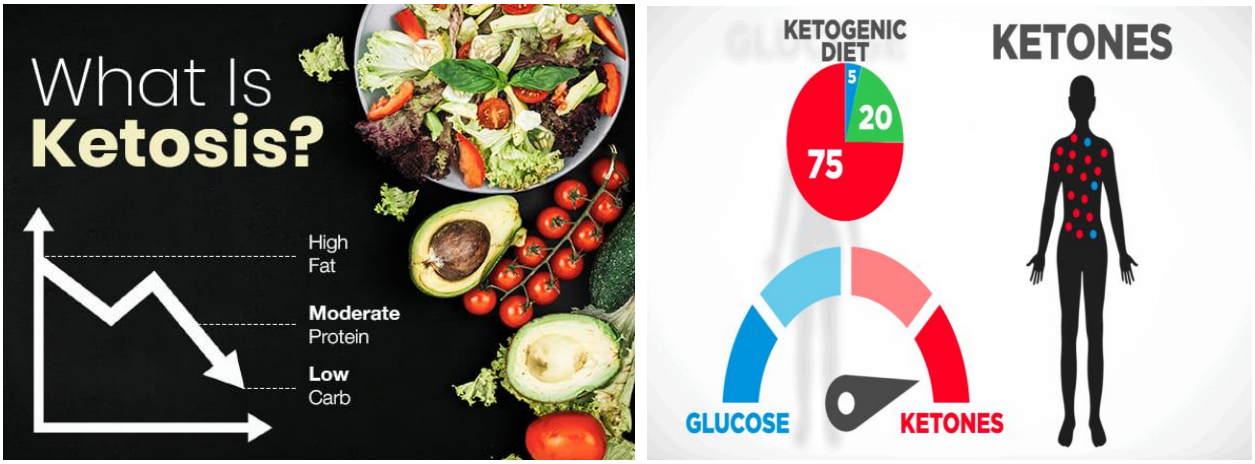

Figure 4: Ketosis.

Outcomes: A study with an intent-to-treat prospective design was published in 1998 by a team from the Johns Hopkins Hospital and followed-up by a report published in 2001. As with most studies of the ketogenic diet, no control group (patients who did not receive the treatment) was used. The study enrolled 150 children. After three months, 83% of them were still on the diet, 26% had experienced a good reduction in seizures, 31% had had an excellent reduction, and 3% were seizure-free. At 12 months, 55% were still on the diet, 23% had a good response, 20% had an excellent response, and 7% were seizure-free. Those who had discontinued the diet

by this stage did so because it was ineffective, too restrictive, or due to illness, and most of those who remained were benefiting from it. The percentage of those still on the diet at two, three, and four years was 39%, 20%, and 12%, respectively. During this period, the most common reason for discontinuing the diet was because the children had become seizure-free or significantly better. At four years, 16% of the original 150 children had a good reduction in seizure frequency, 14% had an excellent reduction, and 13% were seizure-free, though these figures include many who were no longer on the diet. Those remaining on the diet after this duration were typically not seizure-free, but had had an excellent response. It is possible to combine the results of several small studies to produce evidence that is stronger than that available from each study alone—a statistical method known as meta-analysis. One of four such analyses, conducted in 2006, looked at 19 studies on a total of 1,084 patients. It concluded that a third achieved an excellent reduction in seizure frequency and half the patients achieved a good reduction. A Cochrane systematic review in 2018 found and analyzed eleven randomized controlled trials of ketogenic diet in people with epilepsy for whom drugs failed to control their seizures. Six of the trials compared a group assigned to a ketogenic diet with a group not assigned to one. The other trials compared types of diets or ways of introducing them to make them more tolerable. In the largest trial of the ketogenic diet with a non-diet control, nearly 38% of the children and young people had half or fewer seizures with the diet compared 6% with the group not assigned to the diet. Two large trials of the Modified Atkins Diet compared to a non-diet control had similar results, with over 50% of children having half or fewer seizures with the diet compared to around 10% in the control group. A systematic review in 2018 looked at 16 studies on the ketogenic diet in adults. It concluded that the treatment was becoming more popular for that group of patients, that the efficacy in adults was similar to children, the side effects relatively mild. However, many patients gave up the diet, for various reasons, and the quality of evidence was inferior to studies on children. Health issues include high levels of low-density lipoprotein, high total cholesterol, and weight loss.[8]

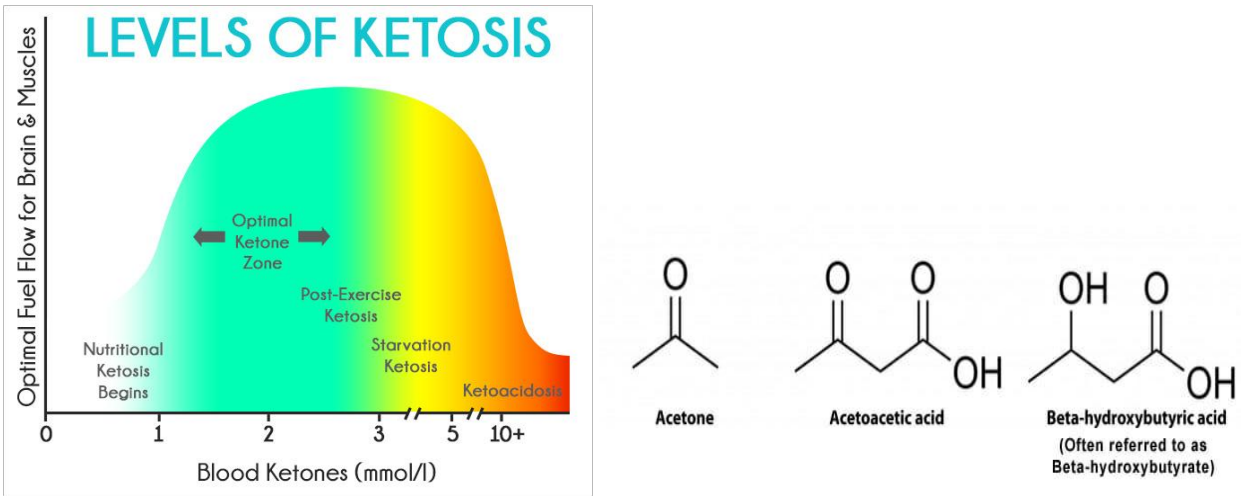

Figure 5: Ketosis Level & Ketone Bodies.

Ketosis is a metabolic state characterized by elevated levels of ketone bodies in the blood or urine. Physiologic ketosis is a normal response to low glucose availability, such as low-carbohydrate diets or fasting, that provides an additional energy source for the brain in the form of ketones. In physiologic ketosis, ketones in the blood are elevated above baseline levels, but the body's acid–base homeostasis is maintained. This contrasts with ketoacidosis, an uncontrolled production of ketones that occurs in pathologic states and causes a metabolic acidosis, which is a medical emergency. Ketoacidosis is most commonly the result of complete insulin deficiency in type 1 diabetes or late-stage type 2 diabetes. Ketone levels can be measured in blood, urine or breath and are generally between 0.5 and 3.0 millimolar (mM) in physiologic ketosis, while ketoacidosis may cause blood concentrations greater than 10 mM. Trace levels of ketones are always present in the blood and increase when blood glucose reserves are low and the liver shifts from primarily metabolizing carbohydrates to metabolizing fatty acids. This occurs during states of increased fatty acid oxidation such as fasting, starvation, carbohydrate restriction, or prolonged exercise. When the liver rapidly metabolizes fatty acids into acetyl-CoA, some acetyl-CoA molecules can then be converted into ketone bodies: acetoacetate, beta-hydroxybutyrate, and acetone. These ketone bodies can function as an energy source as well as signaling molecules. The liver itself cannot utilize these molecules for energy, so the ketone bodies are released into the blood for use by peripheral tissues including the brain. When ketosis is induced by carbohydrate restriction, it is sometimes referred to as nutritional ketosis. A low-carbohydrate, moderate protein diet that can lead to ketosis is called a ketogenic diet. Ketosis is well-established as a treatment for epilepsy and is also effective in treating type 2 diabetes. The

possible effect on a range of neurological diseases, metabolic syndrome, cancer, and other conditions is currently under investigation.

Physiologic ketosis: Physiologic ketosis is a physiologic state characterized by elevated serum ketones and normal blood glucose and blood pH. Increasing production of ketone bodies is a response to low glucose availability that creates an alternate energy source for the brain. Physiologic ketosis can result from any state that increases fatty acid oxidation including fasting, prolonged exercise, or very low-carbohydrate diets such as the ketogenic diet. When physiologic ketosis is induced by carbohydrate restriction, it is sometimes referred to as nutritional ketosis. Ketone levels generally remain below 3 mM.

Ketoacidosis: Ketoacidosis is a pathological state of uncontrolled production of ketones that results in a metabolic acidosis. Ketoacidosis is most commonly caused by a deficiency of insulin in type 1 diabetes or late-stage type 2 diabetes but can also be the result of chronic heavy alcohol use, salicylate poisoning, or isopropyl alcohol ingestion. Ketoacidosis causes significant metabolic derangements and is a life-threatening medical emergency. Ketoacidosis is distinct from physiologic ketosis as it requires failure of the normal regulation of ketone body production.

Causes: Elevated blood ketone levels are most often caused by accelerated ketone production but may also be caused by consumption of exogenous ketones or precursors. When glycogen and blood glucose reserves are low, a metabolic shift occurs in order to save glucose for the brain which is unable to use fatty acids for energy. This shift involves increasing fatty acid oxidation and production of ketones in the liver as an alternate energy source for the brain as well as the skeletal muscles, heart, and kidney. Low levels of ketones are always present in the blood and increase under circumstances of low glucose availability. For example, after an overnight fast, 2-6% of energy comes from ketones and this increases to 30-40% after a 3-day fast. The amount of carbohydrate restriction required to induce a state of ketosis is variable and depends on activity level, insulin sensitivity, genetics, age and other factors, but ketosis will usually occur when consuming less than 50 grams of carbohydrates per day for at least three days. Neonates, pregnant women and lactating women are populations that develop physiologic ketosis especially rapidly in response to energetic challenges such as fasting or illness. This can progress to ketoacidosis in the setting of illness, although it occurs rarely. Propensity for ketone production in neonates is caused by their high-fat breast milk diet, disproportionately large central nervous system and limited liver glycogen.

Biochemistry: The precursors of ketone bodies include fatty acids from adipose tissue or the diet and ketogenic amino acids. The formation of ketone bodies occurs via ketogenesis in the mitochondrial matrix of liver cells. Fatty acids can be released from adipose tissue by adipokine signaling of high glucagon and epinephrine levels and low insulin levels. High glucagon and low insulin correspond to times of low glucose availability such as fasting. Fatty acids bound to coenzyme A allow penetration into mitochondria. Once inside the mitochondrion, the bound fatty acids are used as fuel in cells predominantly through beta oxidation, which cleaves two carbons from the acyl-CoA molecule in every cycle to form acetyl-CoA. Acetyl-CoA enters the citric acid cycle, where it undergoes an aldol condensation with oxaloacetate to form citric acid; citric acid then enters the tricarboxylic acid cycle (TCA), which harvests a very high energy yield per carbon in the original fatty acid.

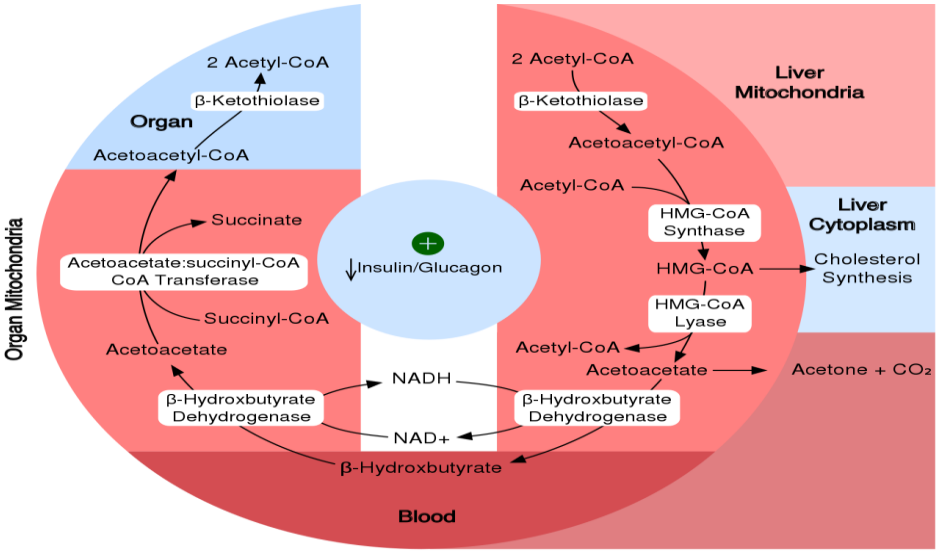

Figure 6: Ketone biosynthesis.

Biochemical pathway of ketone synthesis in the Liver and Utilization by organs: Acetyl-CoA can be metabolized through the TCA cycle in any cell, but it can also undergo ketogenesis in the mitochondria of liver cells. When glucose availability is low, oxaloacetate is diverted away from the TCA cycle and is instead used to produce glucose via gluconeogenesis. This utilization of oxaloacetate in gluconeogenesis can make it unavailable to condense with acetyl-CoA, preventing entrance into the TCA cycle. In this scenario, energy can be harvested from acetyl-CoA through ketone production.

In ketogenesis, two acetyl-CoA molecules condense to form acetoacetyl-CoA via thiolase. Acetoacetyl-CoA briefly combines with another acetyl-CoA via HMG-CoA synthase to form hydroxy-β-methylglutaryl-CoA. Hydroxy-β-methylglutaryl-CoA form the ketone body acetoacetate via HMG-CoA lyase. Acetoacetate can then reversibly convert to another ketone body—D-β-hydroxybutyrate—via D-β-hydroxybutyrate dehydrogenase. Alternatively, acetoacetate can spontaneously degrade to a third ketone body (acetone) and carbon dioxide, which generates much greater concentrations of acetoacetate and D-β-hydroxybutyrate. The resulting ketone bodies cannot be used for energy by the liver so are exported from the liver to supply energy to the brain and peripheral tissues. In addition to fatty acids, deaminated ketogenic amino acids can also be converted into intermediates in the citric acid cycle and produce ketone bodies.

Ketone levels can be measured by testing urine, blood or breath. There are limitations in directly comparing these methods as they measure different ketone bodies.

Urine testing: Test for ketonuria using Bayer Ketostix reagent strips: Urine testing is the most common method of testing for ketones. Urine test strips utilize a nitroprusside reaction with acetoacetate to give a semi-quantitative measure based on color change of the strip. Although beta-hydroxybutyrate is the predominant circulating ketone, urine test strips only measure acetoacetate. Urinary ketones often correlate poorly with serum levels because of variability in excretion of ketones by the kidney, influence of hydration status, and renal function.

Serum testing: Finger-stick ketone meters allow instant testing of beta-hydroxybutyrate levels in the blood, similar to glucometers. Beta-hydroxybutrate levels in blood can also be measured in a laboratory.

Adverse effects: The ketogenic diet is not considered a benign, holistic, or all-natural treatment. As with any serious medical therapy, it may result in complications, although these are generally less severe and less frequent than with anticonvulsant medication or surgery. Common but easily treatable short-term side effects include constipation, low-grade acidosis, and hypoglycemia if an initial fast is undertaken. Raised levels of lipids in the blood affect up to 60% of children and cholesterol levels may increase by around 30%. This can be treated by changes to the fat content of the diet, such as from saturated fats towards polyunsaturated fats, and if persistent, by lowering the ketogenic ratio. Supplements are necessary to counter the dietary deficiency of many micronutrients.

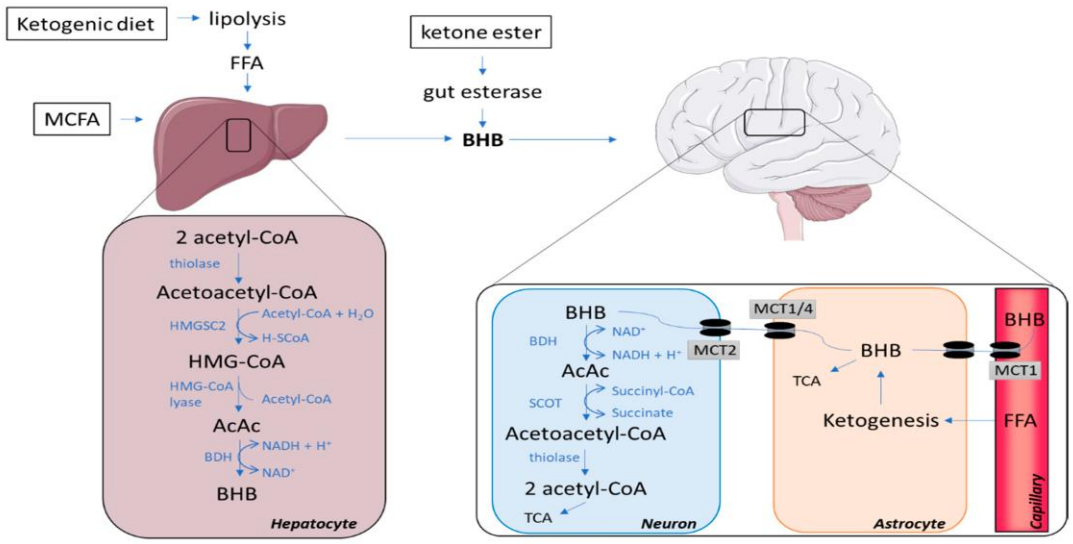

Figure 7: Ketogenesis.

Long-term use of the ketogenic diet in children increases the risk of slowed or stunted growth, bone fractures, and kidney stones. The diet reduces levels of insulin-like growth factor 1, which is important for childhood growth. Like many anticonvulsant drugs, the ketogenic diet has an adverse effect on bone health. Many factors may be involved such as acidosis and suppressed growth hormone. About one in 20 children on the ketogenic diet develop kidney stones (compared with one in several thousand for the general population). A class of

anticonvulsants known as carbonic anhydrase inhibitors (topiramate, zonisamide) are known to increase the risk of kidney stones, but the combination of these anticonvulsants and the ketogenic diet does not appear to elevate the risk above that of the diet alone. The stones are treatable and do not justify discontinuation of the diet. Around half of clinics gives oral potassium citrate supplements empirically to all ketogenic diet patients, with some evidence that this reduces the incidence of stone formation.[9] However, has not been tested in a prospective controlled trial. Kidney stone formation (nephrolithiasis) is associated with the diet for four reasons:

- Excess calcium in the urine (hypercalciuria) occurs due to increased bone demineralization with acidosis. Bones are mainly composed of calcium phosphate. The phosphate reacts with the acid, and the calcium is excreted by the kidneys.
- Hypocitraturia: the urine has an abnormally low concentration of citrate, which normally helps to dissolve free calcium.
- The urine has a low pH, which stops uric acid from dissolving, leading to crystals that act as a nidus for calcium stone formation.
- Many institutions traditionally restricted the water intake of patients on the diet to 80% of normal daily needs; this practice is no longer encouraged. In adolescent and adults, common side effects reported include weight loss, constipation, dyslipidemia, and in women, dysmenorrhea.[10]

CONCLUSION

Although many hypotheses have been put forward to explain how the ketogenic diet works, it remains a mystery. Disproven hypotheses include systemic acidosis (high levels of acid in the blood), electrolyte changes and hypoglycemia (low blood glucose). Although many biochemical changes are known to occur in the brain of a patient on the ketogenic diet, it is not known which of these has an anticonvulsant effect. The lack of understanding in this area is similar to the situation with many anticonvulsant drugs.

On the ketogenic diet, carbohydrates are restricted and so cannot provide for all the metabolic needs of the body. Instead, fatty acids are used as the major source of fuel. These are used through fatty-acid oxidation in the cell's mitochondria (the energy-producing parts of the cell). Humans can convert some amino acids into glucose by a process called gluconeogenesis, but cannot do this by using fatty acids. Since amino acids are needed to make proteins, which are essential for growth and repair of body tissues, these cannot be used only to produce glucose. This could pose a problem for the brain, since it is normally fuelled solely by glucose, and most fatty acids do not cross the blood–brain barrier. However, the liver can use long-chain fatty acids to synthesise the three ketone bodies β-hydroxybutyrate, acetoacetate and acetone. These ketone bodies enter the brain and *partially* substitute for blood glucose as a source of energy.

The ketone bodies are possibly anticonvulsant; in animal models, acetoacetate and acetone protect against seizures. The ketogenic diet results in adaptive changes to brain energy metabolism that increase the energy reserves; ketone bodies are a more efficient fuel than glucose, and the number of mitochondria is increased. This may help the neurons to remain stable in the face of increased energy demand during a seizure, and may confer a neuroprotective effect. The ketogenic diet has been studied in at least 14 rodent animal models of seizures. It is protective in many of these models and has a different protection profile than any known anticonvulsant. Conversely, fenofibrate, not used clinically as an antiepileptic, exhibits experimental anticonvulsant properties in adult rats comparable to the ketogenic diet. This, together with studies showing its efficacy in patients who have failed to achieve seizure control on half a dozen drugs, suggests a unique mechanism of action. Anticonvulsants suppress epileptic seizures, but they neither cure nor prevent the development of seizure susceptibility. The development of epilepsy (epileptogenesis) is a process that is poorly understood. A few anticonvulsants (valproate, levetiracetam and benzodiazepines) have shown antiepileptogenic properties in animal models of epileptogenesis. However, no anticonvulsant has ever achieved this in a clinical trial in humans. The ketogenic diet has been found to have antiepileptogenic properties in rats. The ketogenic diet has been studied for potential therapeutic use in various neurological disorders other than epilepsy: Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), autism, headache, neurotrauma, pain, Parkinson's disease (PD) and sleep disorders.

Because some cancer cells are inefficient in processing ketone bodies for energy, the ketogenic diet has also been suggested as a treatment for cancer. A 2018 review looked at the evidence from preclinical and clinical studies of ketogenic diets in cancer therapy. The clinical studies in humans are typically very small, with some providing weak evidence for an anti-tumour effect, particularly for glioblastoma, but in other cancers and studies, no anti-tumour effect was seen. Taken together, results from preclinical studies, albeit sometimes contradictory, tend to support an anti-tumor effect rather than a pro-tumor effect of the KD for most solid cancers. The evidence of benefit for these conditions has not reached the level where clinical recommendations can be made.

REFERENCE

1. Freeman JM, Kossoff EH, Hartman AL. The ketogenic diet: one decade later. Pediatrics, 2007; 119(3): 535–43.
2. Martin-McGill KJ, Jackson CF, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev.

3. Kossoff EH, Wang HS. Dietary therapies for epilepsy. Biomed J, 2013; 36(1): 2-8.
4. Liu YM. Medium-chain triglyceride (MCT) ketogenic therapy. Epilepsia.
5. Zupec-Kania BA, Spellman E. An overview of the ketogenic diet for pediatric epilepsy. Nutr Clin Pract, 2009; 23(6): 589–96.
6. Gano LB, Patel M, Rho JM. Ketogenic diets, mitochondria, and neurological diseases. J Lipid Res, 2014; 55(11): 2211-28.
7. Pavan Chaudhary, Jainik Khamar and Prof. Dr. Dhrubo Jyoti Sen; Avocado: the holistic source as a natural doctor!: World Journal of Pharmaceutical Research, 2015; 4(8): 748-761.
8. de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. Epilepsy Behav, 2008; 12(4): 540–6.
9. Cai QY, Zhou ZJ, Luo R, Gan J, Li SP, Mu DZ, Wan CM. Safety and tolerability of the ketogenic diet used for the treatment of refractory childhood epilepsy: a systematic review of published prospective studies. World J Pediatr, 2017; 13(6): 528-536.
10. Wheless JW. History and origin of the ketogenic diet (PDF). In: Stafstrom CE, Rho JM, editors. Epilepsy and the ketogenic diet. Totowa: Humana Press, 2004.