

Review on the Benefits and Drawbacks of Ketogenic diet in Humans.

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ABSTRACT

ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that in medicine is used primarily to treat difficult-to-control (refractory) epilepsy in children. The diet forces the body to burn fats rather than carbohydrates to generate energy for the cells through the process of glycogenolysis. In times of fasting, even overnight while sleeping, the amount of ketone bodies in the blood increases. The synthesis occurs primarily in the mitochondria of liver cells. Ketogenesis produces acetone, acetoacetate, and beta-hydroxybutyrate molecules by breaking down fatty acids. ketogenic diet is used clinically to treat seizures, overweight, diabetes and cancer but its negative effect is inevitable thus causing Keto Flu, hunger, headaches, nausea, fatigue, irritability, constipation and brain fog. It is best to consult a dietitian and physician to ensure you are monitoring not just the scale, or how you feel, but what is going on in your body internally with the proper guidance.

Keywords: Ketogenesis, glycogenolysis, Keto Flu

INTRODUCTION

Glucose is a form of sugar that is usually your body's (especially your brain's) main source of energy. When glucose is low, your body dips into your ketones that have been made from ketogenesis for energy. This alternative metabolic process your body switches to is known as ketosis. One job of your liver is to make ketones consistently anyway, but the amount will change based on one's carb and protein intake [1]. The rate of generating ketones slows when it is simply not needed. But with the keto diet, your body doesn't get enough glucose to use it as its fuel. Instead, your body stays in a state of ketosis.

Ketogenic" is a term for a low-carb diet (like the Atkins diet). The idea is for you to get more calories from protein and fat and less from carbohydrates. You cut back most on the carbs that are easy to digest, like sugar, soda, pastries, and white bread [1].

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difficult-to-control (refractory) epilepsy in children. The diet forces the body to burn fats rather than carbohydrates. Normally, the carbohydrates contained in food are converted into glucose, which is then transported around the body and is particularly important in fueling brain function. However, if little carbohydrate remains in the diet, the liver converts fat into fatty acids and ketone bodies. The ketone bodies pass into the brain and replace glucose as an energy source. An elevated level of ketone bodies in the blood, a state known as ketosis, leads to a reduction in the frequency of epileptic seizures [2]. 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 even after discontinuing the diet [3]. Some evidence indicates that adults with epilepsy may benefit from the diet, and that a less strict regimen, such as a modified Atkins diet, is similarly effective [4].

Ketogenesis

Ketogenesis is a metabolic pathway that produces ketone bodies, which provide an alternative form of energy for the body. The body is constantly producing small amounts of ketone bodies that can make 22 ATP each in normal circumstances, and

it is regulated mainly by insulin. In a state of ketosis, ketone body production is increased when there are decreased carbohydrates or increased fatty acids. However, ketoacidosis can occur if too many ketone bodies accumulate, such as

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in cases uncontrolled diabetes [5]. Ketogenesis produces acetone, acetoacetate, and beta-hydroxybutyrate molecules by breaking down fatty acids. These ketones are water-soluble lipid molecules made up of two R-groups attached to a carbonyl group ($C = O$). Because they are water soluble, they do not require lipoproteins for transport. Of the three, acetoacetate and beta-hydroxybutyrate are acidic, having pKa values of 3.6 and 4.7 respectively [6].

Functions

In healthy humans, the body is continually making a small amount of ketones to be used by the body for energy. In times of fasting, even overnight while sleeping, the amount of ketone bodies in the blood increases. The normal pathways to create energy involve either stored carbohydrate or non-carbohydrate substances. When ample carbohydrate stores are available, the main pathway used is glycogenolysis [7]. This involves the breakdown of glycogen stores in muscle and liver. Gluconeogenesis, the production of glucose from non-carbohydrate sources such as lactate, is often utilized as well, especially in situations involving exercise. When carbohydrate stores are significantly decreased, or fatty acid concentration is increased, there is an upregulation of the ketogenic pathway and an increased production of ketone bodies [7]. This can be seen in conditions such as type 1 diabetes, alcoholism, and starvation. Most organs and tissues can use ketone bodies as an alternative source of energy. The brain uses them as a major source of energy during periods where glucose is not readily available. This is because, unlike other organs in the body, the brain has an absolute minimum requirement of glucose [8]. The heart typically uses fatty acids as its source of energy, but also can use ketones. The liver, although the primary site that produces ketone bodies, does not use ketone bodies because it lacks the necessary enzyme beta ketoacyl-CoA transferase [9].

Mechanism of action

The synthesis occurs primarily in the mitochondria of liver cells. Fatty acids are brought into the mitochondria via carnitine palmitoyltransferase (CPT-1) and then broken down into acetyl CoA via beta-oxidation [10]. Two acetyl-CoA molecules are converted into acetoacetyl-CoA via the enzyme thiolase; this is also known as acetyl coenzyme A acetyltransferase (ACAT). Afterward, acetoacetyl-CoA is converted to HMG-CoA via the enzyme HMG-CoA synthase. HMG-CoA lyase then converts HMG-CoA to acetoacetate. Acetoacetate can be converted to either acetone through non-enzymatic decarboxylation, or to beta-hydroxybutyrate via beta-hydroxybutyrate dehydrogenase [11]. Acetoacetate and beta-hydroxybutyrate are the two ketone bodies used by the body for energy. Once they reach extrahepatic tissues, beta-hydroxybutyrate is converted to acetoacetate via the enzyme beta-hydroxybutyrate dehydrogenase, and acetoacetate is converted back to acetyl-CoA via the enzyme beta-ketoacyl-CoA transferase. Acetyl-CoA goes through the citric acid cycle, and after oxidative phosphorylation produces 22 ATP per molecule. Acetone does not convert back to acetyl-CoA, so it is either excreted through urine or exhaled [12].

Regulation of Ketogenesis

Ketogenesis can be upregulated by hormones such as glucagon, cortisol, thyroid hormones, and catecholamines by causing greater breakdown of free fatty acids, thus increasing the amount available to be used in the ketogenic pathway. However, insulin is the main hormonal regulator of this process [13]. Insulin regulates many key enzymes in the ketogenic pathway, and a state of low insulin triggers the process. A low insulin state leads to:

- Increased free fatty acids (FFAs). This is due to decreased inhibition of hormone-sensitive lipase.
- Increased uptake of FFAs into the mitochondria, which is due to decreased activation of acetyl-CoA carboxylase, decreasing malonyl

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CoA, which disinhibits Carnitine Palmitoyltransferase 1 (CPT1).

- Increased production of ketone bodies due to increased HMG-CoA activity

Positive effects ketogenic diet

Epilepsy

The ketogenic diet was first used clinically to treat seizures. It has been used to successfully reduce seizures for many years, with research to back up the benefits outweighing any cons [4].

Weight loss

There are some great metabolic changes initially with this diet. In an article by Antonio Paoli he notes that the health parameters associated with carrying excess weight improve, such as insulin resistance, high blood pressure, and elevated cholesterol and triglycerides. It is true that fat oxidation does increase due to the body adapting to the higher dietary fat intake. However, fat oxidation and losing body fat are two different processes [2]. When fat oxidation is higher it does not necessarily mean that there will be a reduction in body fat.

Negative effect of ketogenic diet

Some negative side effects of a long-term ketogenic diet have been suggested in a review of the diet by Harvard's school of public health, including increased risk of kidney stones and osteoporosis, and increased blood levels of uric acid (a risk factor for gout) [6]. The biggest areas of concern is listed below:

Nutrient Deficiencies

Because whole food groups are excluded, nutrients typically found in foods like whole grains and fruit that are restricted from the diet can lead to deficiencies, especially if the diet is followed incorrectly or without proper guidance. It is vital to incorporate a wide variety of foods while eating such high amounts of fat [12]. Each food group offers different essential nutrition. Focus on meats, seafood, vegetables, some legumes, and fruits to make sure you are getting fiber, B vitamins, and minerals such as iron, magnesium, and zinc. It would be best to consult with a registered dietitian to alleviate the possibility of any deficiencies.

Overall calorie intake and calorie burn will be the main determinant in fat loss.

Type 2 diabetes

Carb restriction can have a direct impact on glucose concentrations, lowering them over time [7]. It may be a straight forward way one could get their diabetes under control. But one should consult a registered dietitian before utilizing this strategy, as a general healthful diet and carb control can produce the same results.

Cancer

This is a growing area of research for the ketogenic diet. The Warburg effect has established that tumor cells can break down glucose much faster (specifically 200x faster) compared to typical cells [9]. The theory is that by "starving" tumor cells of glucose, you can inhibit their growth and help prevent cancer.

Keto Flu

During the diet transition you may experience uncomfortable side effects from significantly cutting carbs, sometimes called the "Keto Flu". Hunger, headaches, nausea, fatigue, irritability, constipation and brain "fog" may last days. Sleep and hydration will help, but it may not be a pleasant transition into the diet [6].

Adherence

Point blank, following a very high-fat diet may be challenging to maintain for most. Keeping yourself satisfied with a limited variety of food and food groups and not being allowed to have some of the more pleasurable foods like fruit, rice dishes, ice cream, or cream based soups may be challenging to maintain. This is very individual, but adhering to healthy diet is important. To truly gain long-term health benefits, one must have healthy habits in place year round, not 30 days at a time [6].

Gut Health

Using the restroom may be difficult since removing whole grain and fruit will

greatly lower ones fiber intake. Not great for gut health [11].

CONCLUSION

In regards to fat loss, someone may try something extreme temporarily, and if it works they can reap those physical benefits correlated with losing body fat. Once the diet is complete there may be a more complex transition or normal eating again. Or, if it is used for the long term, there have not been studies yet to see how this impacts our health. What we do know is that an overall nourishing, vitamin packed diet (or way of eating) should include high quality foods, variety, and the ability to adhere to the diet whether it is for fat loss, muscle gain, or general maintenance. The ketogenic diet is missing some vital food groups, and in turn, vital nutrients. It is best to

consult with a dietitian and physician to ensure you are monitoring not just the scale, or how you feel, but what is going on in your body internally with the proper guidance. As with all nutrition recommendations, they are individual, in relation to a person's health history, preferences, goals, activity level, as well as special health needs. It is the role of the registered dietitian nutritionist to guide clients toward a safe, health-optimizing lifestyle through personalized nutrition. And to stay up to date with the newest and most thorough research. What may work for one, may not for another. And what we know now, may also change in the future.

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