A Review of Ketogenic Diet and Lifestyle

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Although ketogenic diets are popular and patients show great interest, their use must be approached with caution.

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Abstract

The ketogenic diet has become increasing popular in recent years. With 25.4 million unique searches, the keto diet was the most Googled diet in the United States in 2020.[1] With increased consumer interest, the "keto" food industry has grown rapidly, and as a result, the global ketogenic diet market was valued at $9.57 billion in 2019.[2] The ketogenic diet has been discussed in popular culture by celebrities, health magazines, and documentaries. The popularity of this diet, and diets in general may be explained by the obesity epidemic in the United States and Missouri.

Introduction

As of 2018, the prevalence of obesity in this country is 42%.[3] In Missouri, two-thirds of the adult population is overweight or obese.[4] Patients trying to lose weight often turn to popular diets, and in the past few years, the ketogenic diet has been a trendy option. With the increased interest in this diet, researchers are working to understand the impact of this pattern of eating on patients' health. There is evidence of benefit, especially regarding weight loss, but there are also risks and concerns. The goal of this review is to offer clarity to physicians counseling patients on the ketogenic diet with the latest literature about benefits and risks.

History of the Ketogenic Diet

In 1911, the first modern use of starvation for the treatment of epilepsy was noted. Two physicians in Paris reported that seizures were less severe in period of starvation.[5] While this was the origin for the ketogenic diet, it wasn't until 1921 that any physician tried to generate ketosis. Dr. Rollin Woodyatt noted that under conditions of starvation, acetone, and beta-hydroxybutyric acid appear.[5] Woodyatt also uncovered that acetone and beta-hydroxybutyric acid were observed if patients ate a low carbohydrate diet. Around the same time, Dr. Russell Wilder theorized that ketonemia could be produced for therapeutic benefit, but with a low carb diet rather than starvation.[5] He developed the term "ketogenic diet." The ketogenic diet become very popular in the treatment of childhood epilepsy.[5] As better epilepsy medications were developed throughout the twentieth century, the ketogenic diet lost prominence as an epilepsy treatment.

In the 1970s, nutritional ketosis was introduced as an idea for weight loss by Dr. Robert Atkins. In his book published in 1972, he describes how reducing carbohydrates "creates a unique chemical situation in the body…ketones are excreted, and hunger disappears."[6] Although the Atkins diet was one of the first, many other low carb diets have been popularized since

the 1970s, from the South Beach Diet to variations of the Paleo and Mediterranean diets. While the details of low-carbohydrate diets may have changed, they have remained a mainstream option for weight loss. Over the past few decades, many studies have sought to quantify the efficacy of low carb diets in terms of weight loss as well as evaluate the potential for amelioration of chronic disease. As research has investigated the mechanisms behind ketosis and weight loss, the ketogenic diet has become the de facto low carb diet of choice in the media and public dialogue.[1]

What is the Ketogenic Diet?

The mainstay of the ketogenic diet is that dietary carbohydrates are kept very low, with varying levels of protein and fat. The classic ketogenic diet is defined as a diet with one gram protein per kilogram of body weight, 10-15g carbohydrates per day, and the remaining calories from fat.[7] The goal of the diet is to induce ketosis. Ketosis is thought to alter metabolic pathways to induce weight loss and potentially improve other health outcomes, such as a reduction of hyperglycemia and improvement in lipid profiles.

What is Ketosis?

Under ordinary circumstances, the body primarily relies on carbohydrates for energy production. Insulin functions to extract and store energy derived from glucose. When the body has reduced carbohydrates available, insulin secretion is reduced. Initially, stored glucose in the form of glycogen is available for fuel, but after three to four days, this is depleted. Stored fat then becomes the most readily available fuel, and its breakdown into free fatty acids provides the raw materials for ketone production in the liver. Ketone production is primarily seen in times of starvation and prolonged exercise, but is also a function of adherence to a very-low carbohydrate diet. Importantly, in physiological ketosis, there is no change in blood pH versus pathological ketosis where there is a lowering of blood pH.

Ketogenic Diet Weight Loss Mechanisms

There is evidence that the ketogenic diet is an effective weight loss therapy. However, the exact mechanisms behind this weight loss remain unclear. For example, in a review of thermodynamic principles of weight loss, Feinman and Fine explain that low-carbohydrate diets have decreased insulin fluxes causing an increased rate of lipolysis.[8] In other words, insulin inhibits lipolysis, and decreased insulin in low-carb diets causes increased fat breakdown.[8] This theory is demonstrated in a study that follows 15 subjects for 12 weeks. The first six weeks they ate a low-carbohydrate diet and the next six weeks a low-fat diet. Blood results after the low-carbohydrate diet displayed decreased circulating triacylglycerol levels versus the low-fat diet.[9] This reiterates the idea that low-carb diets increase fat breakdown.[9]

Another proposed weight loss mechanism is with decreased carbohydrate intake, the body will have to undergo increased amounts of gluconeogenesis to provide glucose to the brain.[10] Gluconeogenesis is an expensive metabolic process.[10] Theoretically, restricting carbohydrates depletes glucose stores, and increases gluconeogenesis.[10] Another mechanism of weight loss is theorized to be direct appetite suppression. In a study with 17 men, subjects were given a high protein diet with two weeks of high-carb and two weeks of moderate-carb intake. During the low-carb, ketogenic diet phase, the participants reported significantly decreased hunger, leading the authors to hypothesize that ketosis itself may suppress hunger.[11] While these mechanisms provide insight into how the ketogenic diet promotes decreased appetite and fat loss, it is important to note that evidence shows weight loss from the ketogenic diet can be partially attributed to water loss. In another study, 20 obese subjects were followed for four months on a ketogenic diet. Utilizing body composition assessments, investigators noted a substantial reduction in weight due to free water loss early in the study.[12] It is important to look at length of duration in ketogenic diet studies as early, dramatic weight loss may be due to diuresis.

With these mechanisms in mind, numerous studies have evaluated the keto diet's weight loss efficacy. There are many examples of randomized controlled trials where significant weight loss is achieved. For example, a meta-analysis by Mansoor et al. looked at mean weight loss in 11 randomized controlled trials for six months with a total of 1,369 participants. In the trials analyzed, participants were randomized into low carbohydrate versus low-fat diet plans. This study found that compared to low-fat diets, low-carbohydrate diets participants lost 2.17 kg more than the low-fat diets (95% CI -3.36, -0.99).[13] However, the duration of some included studies was only six months. When looking at studies with a longer duration, the

weight loss is less superior. For example, in a meta-analysis by Bueno et al., they analyzed 13 randomized controlled trials with a total of 1,415 subjects that were followed for at least 12 months. Again, the very-low-carbohydrate ketogenic diet was compared to a low-fat diet. After twelve months, subjects adhering to the ketogenic diet had lost 0.91 kg compared to the low-fat diet arm (95% CI -1.65, -0.17).[14] While this was a significant result, the weight loss is less than what is seen in the shorter trials.

An interesting perspective is seen in a retrospective analysis of 89 subjects who were followed for 12 months. Subjects followed a diet plan which cycled between shorter periods of a ketogenic Mediterranean diet followed by longer periods of a traditional Mediterranean diet. For a majority (88.25%) of subjects there was substantial weight loss 100.7 ± 16.54 to 84.59 ± 9.71 kg.[15] This study gives a good example of a weight loss regimen that patients may find more feasible. It combines benefits of the ketogenic diet's short-term effects, with a maintenance diet that is less restrictive.

Ketogenic Diet and Diabetes Mellitus

Before the advent of insulin, diet was a mainstay in type 1 diabetes treatment. Famously Dr. Frederick Allen used a low-carbohydrate starvation diet to treat diabetes.[16] However, the use of such diets decreased with the discovery of insulin. More recently, there has been significant interest in the use of ketogenic diets to treat type 2 diabetes in conjunction with obesity. There are several proposed mechanisms that support the use of ketogenic diets to improve hyperglycemia. Most importantly, decreased circulating glucose and increased insulin sensitivity.[17]

Testing this hypothesis, investigators have looked to see if the ketogenic diet can help improve hyperglycemia. One small, shorter study recruited 28 participants to follow for 16 weeks. In this study all 28 subjects that were enrolled received ketogenic diet counseling with a goal of less than 20 grams of carbohydrates per day. At the end of the 16 weeks, 21 participants had completed the trial. The mean fasting glucose decreased by 16.6% from 9.08 ± 4.09 mmol/L at baseline to 7.57 ± 2.63 mmol/L at week 16 ($p = 0.04$).[18] The hemoglobin A1c decreased from 7.5 ± 1.4% at baseline to 6.3 ± 1.0% at week 16 ($p < 0.001$).[18] These results were encouraging, but with short duration and small sample size.

In a two-year, open label, non-randomized, controlled study, 349 participants received either standard care or were educated to follow a ketogenic diet.[19] At the end of two years, those who had followed diets to stimulate ketosis had a 0.9% decrease in HbA1c versus a 0.4% increase in the standard of care arm. In addition, those following the ketogenic diet decreased their use of diabetic medications by 81%, while medication use increased in standard of care patients.[19] Another similar trial looking at glycemic control outcomes after two years showed no significant difference in HbA1c levels between the low-fat and low-carbohydrate groups.[20] These studies show than in the shorter term, there seem to be clinically significant improvements in glycemia control outcomes. However, in the longer term, while there are examples of improved HbA1c and medication use, there is less extreme improvement.

A very recent meta-analysis by Goldenberg et al. evaluated the efficacy of low-carb and very-low-carb diets in type 2 diabetes that seemed to support the idea that while significant benefit in weight loss, glycemic control, and insulin sensitivity were seen in the short term, the benefits seemed to wane after 12 months.[21] Participants in some trials seemed to struggle with adherence to the very-low-carb diet, suggesting that loss of efficacy in longer studies may be related to difficulty in maintaining such a restrictive eating pattern over a long period of time.[21]

It is important to understand the impact of the ketogenic diet in patients with type 1 diabetes. Although it has not been studied extensively, there have been trials showing positive outcomes. One small trial with ten participants were randomized into a carbohydrate restricting arm versus a standard carbohydrate counting arm. They were followed for 12 weeks. At the end of 12 weeks, the carbohydrate restricted arm had significant reductions in HbA1c (8.9 to 8.2%, $p<0.05$) and a significant decrease in daily insulin use (64.4 to 44.2 units per day $p<0.05$).[22]

A critical point to mention is the hypoglycemic risk of the ketogenic diet in the type 1 diabetes population. In an observational study with 11 participants, subjects were followed on a ketogenic diet for three years. A main finding of this study was that participants had 6.3 episodes of hypoglycemia per week compared to on to two episodes a week, noted in previous literature.[23] Of similar concern, there are case studies indicating that the ketogenic diet in people with type 1 diabetes

can precipitate ketoacidosis.[24] Thus, significant caution would need to be observed in patients with type 1 diabetes who wish to follow a ketogenic diet.

Ketogenic Diet and Cardiovascular Disease

A common concern physicians have with the ketogenic diet is its effect on blood lipids and lipoproteins, and more broadly, its effect on cardiovascular disease risk factors. Despite the frequent concern that the ketogenic diet increases LDL-cholesterol, a recent comprehensive review of evidence by the National Lipid Association Task Force, showed variable responses of LDL-cholesterol.[25]

The meta-analysis by Mansoor et al. evaluated cardiovascular risk factors in addition to weight loss as noted above. They evaluated 11 randomized controlled trials with 1,369 participants placed into ketogenic versus low-fat diet arms. They found that the ketogenic diet participants, after six months, had decreased blood triglycerides (-0.26 mmol/l; 95% CI -0.37, -0.15), but an increase in both HDL-cholesterol (0.14 mmol/l; 95% CI 0.09, 0.19) and LDL-cholesterol (0.16 mmol/l; 95% CI 0.003, 0.33).[13]

In another meta-analysis, the authors reviewed eight randomized controlled trials lasting six months with 1,633 participants in a ketogenic versus low-fat randomization. In this analysis, they found no significant difference in LDL-cholesterol levels between groups (0.07 mmol/L; 95% confidence interval [CI], 0.02–0.13; P <0.009] [26]. HDL-cholesterol and plasma triglycerides at six and 12 months increased and decreased, respectively (0.08 mmol/L; 95% CI, 0.06–0.11; $P < 1 \times 10–5$ and –0.13 mmol/L; 95% CI, –0.19 to –0.08; $P < 1 \times 10–5$).[26]

Further analysis suggests that the variation in diet composition may have a significant effect on the lipid changes seen. The increase in LDL-cholesterol seen in some of the randomized controlled studies may be due to the increased intake of saturated fats when carbohydrates are lowered. One meta-analysis centered on randomized controlled trials analyzed long-term effects of low-fat versus high-fat diets. The meta-analysis included 32 studies with 8,862 participants that were followed for a minimum of 12 months. Results showed a decrease in total cholesterol (-4.55 mg/dL; 95% CI -8.03 to -1.07; p=.01) and LDL-cholesterol (-3.11 mg/dL; 95% CI -4.51 to -1.71; p<0.0001) were more prominent in the low-fat arm.[27] Further analysis showed that lower total and LDL-cholesterol were associated with lower saturated fat intake, and increased monounsaturated fat was related to high HDL-cholesterol and lower saturated fat intake.[27]

In summary, there are enough randomized controlled studies showing increased LDL-cholesterol in the ketogenic diet for it to be a consideration in certain patient populations. However, when looking at meta-analyses, the LDL-cholesterol response is variable. Diet composition likely plays an important role in the lipid changes seen in patients adhering to a ketogenic diet, so a high-quality diet with adequate intake of fruits and vegetables and low intake of saturated fats would be preferred. Ketogenic diets have been shown to repeatedly decrease triglycerides and increase HDL-cholesterol levels.

Ketogenic Diet in Pregnancy

There is evidence that women who become pregnant on low-carbohydrate diets have increased risk of birth defects. The National Birth Defects Prevention Study retrospectively looked at mothers with infants with stillbirths, anencephaly, or spina bifida (1,740) versus mothers with infants without defects (9,545). They found that women with restricted carbohydrate intake, defined as less than the fifth percentile among the control group were 30% more likely to have infants with neural tube defects (Odds ratio of 1.30, 95% (1.02, 1.67) p<.01) as well as decreased folic acid levels.[28] Women who plan to become pregnant should be advised to avoid restrictive low-carbohydrate diets. Adequate folate supplementation should be stressed if they choose to continue with a low-carb diet.

Conclusion

Although ketogenic diets are popular and patients show great interest, their use must be approached with caution. There is data showing impressive short-term weight loss, but most analyses suggest that long-term, their efficacy is comparable to other hypocaloric diets. At least part of this effect may be due to difficulty with long-term adherence to such a restrictive eating pattern. In addition, some of the weight lost during the acute period of following a ketogenic diet may be related to water loss, rather than true fat loss. Thus, the impressive short-term weight loss numbers may appear inflated. For patients with type 2 diabetes, it is likely that any weight loss achieved with the ketogenic diet could lower A1c and help reduce the

medication burden. Care must be taken to taper diabetes medications appropriately to reduce the risk of hypoglycemia.

Lastly, long-term safety and health have yet to be proven, especially with regard to lipid profile alterations and cardiovascular impact. Studies generally show improvement in HDL and triglycerides, but LDL response is variable. This may be due to significant variability in the content of the diet of each specific person. Those interested in the keto diet should be encouraged to limit saturated fat and ensure adequate consumption of fruits and vegetables in order to maintain micronutrient and fiber intake.

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Disclosure

None reported.

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