

Ketogenic Diet Role in Management of Type 2 Diabetes Mellitus

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Abstract

The prevalence of type two diabetes (T2D) has been increasing sharply worldwide. Many recent studies have been done to determine the effective strategies for better management of type two diabetes. One of these strategies was the Ketogenic Diet, which when performed on rats and human showed very impressive results. The benefits of having some ketone bodies circulating in the body have numerous benefits such as weight loss, improvement of HbA1c levels, reversal of nephropathy, cardiac benefits and treatment for dyslipidemia.

Keywords: Ketogenic diet; Diabetes; Cardiology; Nephrology

Introduction

According to the latest data by the World Health Organization, approximately 366 million people will have diabetes by the year 2030 [1]. Several studies have shown a strong association between being overweight and the risk of developing diabetes. In fact, according to the US center for Disease control and Prevention, 85% of the diabetic patients are overweight and 55% are obese [2]. For weight loss, it became well known that the energy intake should be decreased and the energy expenditure should be increased. Several interventions have been proposed for decreasing energy intake such as bariatric surgeries, pharmacological usage, and decreasing caloric intake while enhancing energy expenditure to achieve weight loss [3]. Yet, recent studies showed that most of the obesity interventions tend to fail in the long term, especially those that have previously focused on reducing dietary fat [4]. However, recently, several studies have showed the benefits of ketogenic diet in overweight diabetic population [2-14]. This review will discuss the physiological foundation of ketogenic diet and their effects on patients with type 2 diabetes.

Discussion

Physiological aspect of ketogenic diet

Ketogenic diet is a diet that is very low in carbohydrates which results in high circulation of ketone bodies in the body. Usually after 3 days of fasting, or having a dietary intake of carbohydrates less than 20 grams per day, fat oxidation through Krebs cycles will be stopped due to the lack of production of oxaloacetate since glucose is needed with pyruvate carboxylase for the carboxylation of pyruvic acid through ATP to produce oxaloacetate [4].

Moreover, the central nervous system requires glucose as an energy source and thus following a ketogenic diet will cause the need for an alternative energy source which is derived from the overproduction of acetyl-CoA namely ketone bodies. Ketone bodies are made up of acetoacetate, B-hydroxybutric acid and acetone. This whole process occurs in the matrix of liver and is called ketogenesis. Under normal diet, the concentration of ketones bodies is less than 0.3 mmol/l and ketone bodies will not be used as an energy source by the central nervous system until this concentration reaches 4 mmol/l, similar to the glucose concentration. At that point, ketone bodies are then used as a source of energy by the all tissues. Specifically, B-hydroxybutric acid is transformed into acetoacetyl-coA which is then transformed into two molecules of acetyl-coA which are used in Krebs cycle. The maximum ketone bodies concentration in individuals following the ketogenic diet will reach to 8 mmol/l [4].

However, it is important to note that glucose is also formed from two sources: glycogenic amino acids and glycerol. In fact, after few days of complete fasting, glycerol can produce around 60% of the body glucose [4].

Benefits of ketogenic diet with type 2 diabetes

Several studies have shown the benefits of ketogenic diet for patients with type two diabetes, such as weight loss, reducing hbaA1c, reversing nephrology, cardiac benefits, improvement of lipid profile and even have potential effect on reversing diabetic neuropathy and retinopathy [5].

Weight loss

Achieving weight loss is one of the earliest strategies used for the management of type two diabetes and the prevention of diabetic complications. Moreover, there is a positive correlation between ketogenic diet and weight loss. In fact, according to the study done by Sahama et al., which compared the efficacy of ketogenic diet and that of low fat diet, it showed that the ketogenic diet are 3 times more effective in weight loss than the low fat diet [6]. One of the reasons for such weight loss is the excessive fatty acid metabolism in the presence of ketone bodies. Another possible reason for weight loss using ketogenic diet might be the hunger-reduction caused by the hypothalamus, yet the main mechanism is still elusive since ketone bodies have shown to act both anorexigenically and orexigenically. Therefore, more studies should be conducted to determine the mechanism of ketone bodies regarding satiety and appetite reduction.

An observational study done by Leonetti et al., showed that very low carbohydrate ketogenic diet (VLCKD) was effective and safe in morbidly obese patient with or without T2DM scheduled for laparoscopic bariatric surgery. Introducing VLCKD immediately prior to bariatric surgery showed temporary but significant pre-operative weight loss that is helpful in reducing the perioperative risk and difficulties associated with anaesthesia and surgery without the possible disadvantages of carbohydrate withdrawal in close proximity of surgery [7].

Reduction of Hba1c levels

Reduction of the HbA1c levels is one of the main guideline for the management of T2D. Having constantly low levels of hba1c, would decrease the risk of developing diabetic complications. The benefits of carbohydrates restriction in diabetes are immediate and well documented but the concern is about the long term safety and efficacy. These benefits can be achieved even in the absence of weight loss [8].

Histologic studies presented in an experimental study done on rats by Khalifa et al. supported the view that VLCKD has a significant beneficial effect in improving the diabetic state by stabilizing hyperglycemia that could result in improved B-cell function [9].

According to the study done by Talib et al., the effectiveness of ketogenic diet was more significant than that of a low calorie intake diet on the glycosylated hemoglobin. This effect on HbA1c levels is possibly due to the ability of ketone bodies to decrease the glucose metabolism. However, the mechanism of the reduction of glucose metabolism by ketone bodies is still debatable [10].

A review done by Feinman et al., presented many points of evidence to support the use of VLCKD as the first approach in treating T2DM and are effective as an adjunct to pharmacologic therapy in T1DM [8].

Reversing nephropathy

Nephropathy is one of the complications that occur with people with uncontrolled diabetes. A study that was done by Poplawski et al., on rats, showed that ketogenic diet reverses diabetic nephropathy by raising blood levels of 3-beta-hydroxybutyric acid (3-OHB) which subsequently reduce glucose metabolism in at least some tissues including kidneys. Within one week of administration of ketogenic diet to rat, blood glucose got normalized. Remarkably, within 2 months, albumin/creatinine ratio was back to normal and diabetic nephropathy was completely reversed. This reversal in functional nephropathy was associated with robust normalization of expression of genes induced by oxidative and other forms of stress [5]. According to the study done by Talib et al., on human, the ketogenic diet showed decrease in creatinine level compared to the low calorie intake levels which showed increase in creatinine level [10]. Furthermore, it was well established that ketones can be used as an alternative energy-efficient fuel. In fact, according to study Little JR et al., in which B-hydroxybutyric acid infusion were done in dogs, the utilization of ketone accounted for more than 50% of QO2. Therefore, ketogenic diet might have benefit renal functions [11].

Cardiac benefits

Several studies showed the increased risk of cardiovascular disease in diabetic patients. Myocardial dysfunction in diabetes is due to the combination of diabetic cardiomyopathy, myocardial ischemia, and hypertension. There are several factors that cause diabetic cardiomyopathy such as: autonomic dysfunction, interstitial fibrosis, increase in oxidative stress, mitochondrial dysfunction and myocardial stiffness due to persistent hyperglycemia with glycation of interstitial protein. Generally, 95% of the myocardial energy is derived from mitochondrial oxidative metabolism. During fasting and settings of insulin resistance, free fatty acids are the dominant myocardial fuel for oxidative metabolism. An increased reliance on free fatty acid for myocardial fuel at the level of left ventricular function would result in decreased cardiac efficiency and increase propensity for heart failure. However, when serum ketone levels increases, ketone bodies will be a main contributor to myocardial energy metabolism. According to a study done on rat heart model, addition of ketone bodies lead to increased cardiac work efficiency by 25%. Moreover, according to proteomic analysis in mouse models of heart failure done by Aubert et al, and according to metabolomics analysis of end-stage of heart failure in human done by Bedi et al., ketone bodies are the major fuel in failing heart [12-13]. IN EMPA-REG study that was done to show the benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitor on CV and all-cause mortality and hospitalization for heart failure, a failing myocardium may have the ability to use ketone bodies. In conclusion, increase in ketone bodies would lead to increase in cardiac work efficiency, increase in myocardial contractility and thus decrease the incidence and progression of heart failure [14].

Lipid profile

One of the main complication of T2D is cardiovascular disease. Dyslipidemia is considered one of the risk factors of cardiovascular disease. However, several studies showed improvement of lipid profile through ketogenic diet intake. In fact, according to the study done by Talib et al., ketogenic diet showed a significant decrease and low density lipoprotein level, triglyceride and increase in high density lipoprotein levels [10]. Moreover, according to the study done by Sahama et al., ketogenic diet produces a greater reduction of the triglyceride levels when compared to low fat diet [6].

Disadvantages of ketogenic diet

Although this review presented the fact that the pathologies caused by diabetes can be reversed by a simple dietary manipulation. Yet, attention should be driven to the possible disadvantages of this type of diet specially when applied for long duration. First, the ketogenic diet could be too extreme for chronic use in adult patients since it may produce unwanted iatrogenic effects. Patients with T2DM on oral hypoglycemic agents who were put on ketogenic diet were at increased risk of developing hypoglycemia, so reducing the dose of the hypoglycemic agents should be considered [8].

For those scheduled for bariatric surgery who were put on low carbohydrate ketogenic diet, an increased metabolic side effects were more compared to those who were not put on such a diet due to the fact that in the perioperative period there is an increased catabolic state and increased oxidative stress that may have a negative effect on the surgical outcome [7].

Conclusion

In conclusion, Ketogenic diet has several benefits on the management of type two diabetes. These benefits include the reduction of HbA1c level, weight loss, and improvement of lipid profile, cardiac benefits, reversibility of nephropathy and even possible effect on reversing diabetic neuropathy and retinopathy.

Future studies should be conducted on a large population of patients to fully understand the mechanism of action between ketone bodies and the above benefits as well as the possible long-term disadvantages of applying such a diet regimen.

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