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A Review on The Effect of The Ketogenic Diet on Health

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Abstract

A ketogenic diet refers to a diet that produces ketones. A ketogenic diet mimics fasting metabolism without drastically reducing calories. In a Ketogenic diet, blood lipid metabolism is a major concern. In addition to inhibiting glycolysis and fatty acid synthesis, ketone bodies activate peroxisome proliferator-activated receptors. As a result, KBs decrease glycolytic ATP production and promote mitochondrial oxidative metabolism, benefiting downstream metabolic pathways. Despite preserving strength, muscle mass, and resting metabolic rate, the very-low-calorie ketogenic diet reduces body weight, fat mass, and visceral fat. Ketogenic diets can cause hypertriglyceridemia, hyperuricemia, hypercholesterolemia, hypomagnesemia, and hyponatremia if consumed for an extended period of time. KD variants have been found to increase adherence, but further modifications must be made to enhance efficacy, and tolerability, and minimalize adverse effects, depending on the disease.

Keywords: *Ketogenic diet; Ketogenic process; Diabetes mellitus; Cancer; Obesity*

1. Introduction:

Since the beginning of the 20th century, ketogenic diets have been used for treating drug-resistant epilepsy in humans, specifically in children. They are low in carbohydrates and proteins and high in fat (Polito et al., 2023). In 1921, Russel Wilder developed the term "ketogenic diet" to describe a diet that produces ketones (Zhu et al., 2022). Particularly, the ketogenic diet mimics the metabolic effects of fasting without reducing calories significantly. Before introducing antiepileptic agents, such as diphenylhydantoin, the KD was a popular medical approach for treating epilepsy (Zhu et al., 2022). There has been considerable interest in KD in recent decades because of its beneficial effects on numerous diseases, such as neurological disorders, obesity, type 2 diabetes, cancer, intestinal disorders, and respiratory compromise (Casanueva et al., 2020).

In a ketogenic diet, there is an emphasis on fats, moderate protein, and very low carbohydrates (Zhu et al., 2022). Carbohydrates are the most important source of energy for our bodies. A diet low in

carbohydrates, less than 50g per day, reduces insulin secretion and leads to a catabolic state in the body (Polito et al., 2023). The body undergoes certain metabolic changes when glycogen stores are depleted (Polito et al., 2023). In low carbohydrate conditions, two metabolic processes take place: glucose synthesis and ketogenesis. Gluconeogenesis occurs in

the body, usually in the liver, when it produces glucose from lactic acid, glycerol, and the amino acids glutamine and alanine (Masood et al., 2022).

If glucose availability continues to decrease, endogenous glucose production becomes insufficient, so ketogenesis produces ketone bodies in place of glucose to meet the body's needs (Masood et al., 2022). Ketones synthesized by the body can easily be used as energy by the heart, lungs, and kidneys (Cantrell and Mohiuddin, 2022). Additionally, the brain can use ketones as a source of energy when it crosses the blood-brain barrier (Cantrell and Mohiuddin, 2022). Masood et al., 2022 describe how the resting basal metabolic rate (BMR) influences ketones production. There is a greater production of adenosine triphosphate in ketones as compared to glucose, sometimes referred to as a "super fuel." (Masood et al., 2022). This article provided a comprehensive overview of the KD, covering its clinical effects, relevant mechanisms, and implementation across a variety of therapeutic scenarios.

2. Metabolic impact of a ketogenic diet

A major concern during the Ketogenic diet is the metabolism of blood lipids (Noain et al., 2020). Glycolysis generates most of the cell energy by metabolizing glucose into pyruvate, which is then oxidatively phosphorylated in mitochondria (Zhu et al., 2022). The degradation of fatty acids produces energy in the absence of glucose (Zhu et al., 2022). In terms of liver fat metabolism, limiting exogenous fats can effectively reduce liver fat storage by limiting total and saturated fats in the diet (Zhu et al., 2022). Animal and clinical studies have recently demonstrated that cutting carbohydrates can reduce total cholesterol, raise HDL levels, and lower blood TG levels (Feingold, 2021). KD may benefit our health in terms of these cardiovascular risk factors (Noain et al., 2020).

3. Ketogenic process

The liver produces Ketone Bodies (KBs) when it produces excessive levels of acetyl-CoA and oxidizes fats (McDonald & Cervenka, 2018). It can also be used to produce acetoacetate, which can then be converted spontaneously to 3-hydroxybutyrate (Newman & Verdin, 2014). Brain, heart, and muscle can utilize KBs to produce cellular energy in mitochondria once they enter the bloodstream (Achanta, & Rae, 2017; McCue, 2010). A high level of circulating KB produces ketonemia and ketonuria (Paoli et al., 2014). Diabetes ketoacidosis is caused by insulin deficiency, thereby raising plasma KB levels and decreasing blood pH in patients with diabetic ketoacidosis (Paoli et al., 2014). Energy is obtained from

KBs more efficiently than glucose and it is metabolized rapidly (Elamin et al., 2017). Furthermore, KBs inhibit glycolysis

and fatty acid synthesis as well as activate the peroxisome proliferator-activated receptor (Cullingford, 2004). Therefore, KBs reduce glycolytic ATP production and promote mitochondrial oxidative metabolism, which benefits downstream metabolic pathways (Veyrat-Durebex, et al., 2018).

4. Ketogenic Diets as treatment of different diseases

Casanueva et al., 2020 reported that very-low-calorie ketogenic diets (VLCKD) reduced body weight, fat mass, and visceral fat mass while maintaining muscle mass, strength, and resting metabolism. According to one study, people on keto diets lose 2.2 times more fat than those on low-calorie low-fat diets (Bansal et al., 2017). In addition, triglycerides and HDL lipids have increased. Furthermore, the UK Obesity Nutritional Guidelines were compared with a low-carb diet (Fomichev & Nikanova, 2017). There was an average weight loss of 6.7 kg among the minimal-carb category, and 2.3 kg for the minimal-fat category (Fomichev & Nikanova, 2017).

According to Shalabi et al., 2021, most people adopted the ketogenic diet for one to six months, which indicates that it is only a short-term weight loss solution. It was clear that the ketogenic diet was effective in reducing body weight for almost all participants. Several symptoms and side effects were also reported, especially during the first few days of dietary change. Moreover, most of the respondents recommended a ketogenic diet to anyone who wanted to lose weight.

There is chronic hyperglycemia associated with type 2 diabetes mellitus, characterized by fasting plasma glucose levels of 126 mg/dL and glycated hemoglobin concentrations of 6.5% (American diabetes, 2017). The major contributor to high blood glucose levels is dietary carbohydrates, so reducing dietary carbohydrate intake is logical in treating T2DM. Studies have found that carbohydrate restriction reduces postprandial glucose levels and HbA1c levels the most (Crosby et al., 2021). According to a study comparing the effects of a very-low-carbohydrate ketogenic diet (VLCKD) on diabetic patients' blood glucose levels, the VLCKD group had a greater decrease in blood glucose levels over the low-calorie diet group over a period of 24 weeks. A KD treatment improves glycemic control in patients with T2DM by lowering glucose uptake and increasing insulin sensitivity (Crosby et al., 2021).

Based on the Warburg effect, a ketogenic diet has been recommended for cancer patients to regulate glycolysis and increase glucose uptake, while converting glucose to lactate preferentially (Huebner et al., 2014; Liberti et al., 2016). The ketogenic diet stresses cancer cells theoretically by nearly eliminating glucose.

4.1 Adverse Effect of Ketogenic diet

During the first few weeks of following the most restrictive ketogenic diet for epilepsy, fatigue, headaches, nausea, constipation, hypoglycemia, and acidosis may occur. Hypertriglyceridemia, hyperuricemia, hypercholesterolemia, hypomagnesemia, and hyponatremia are also possible complications (Włodarek, 2019; Kang et al., 2004). Anemia, nephrolithiasis, cardiomyopathy, and optic nerve neuropathy are among the long-term effects (Włodarek, 2019). Several studies have shown that ketogenic diets are not sustainable over the long term, as they have low long-term tolerability (Kosinski and Jornayvaz, 2017; Brouns, 2018). Low-carbohydrate diets are also associated with an increased mortality risk, although recent data suggest either a higher mortality risk or a lower mortality risk can be associated with a lower-carbohydrate diet. There may also be an influence on the quality of the carbohydrate content in their food based on the type of carbohydrate and how much protein or fat they contain (Crosby et al., 2021).

5. Conclusion

The ketogenic diet is a well-established first-line treatment for obesity and type 2 diabetes based on available evidence. Other chronic, sometimes intractable, metabolic disorders are also likely to be improved with a ketogenic diet, such as type2 diabetes, obesity, and cancer. Although the KD has adverse effects, it is usually not long-term tolerable, causing less compliance by patients and caregivers, as well as impairing the clinical efficacy of treatment. The use of several KD variants is proven to increase adherence, but additional modifications are still required and should be tailored to specific diseases to enhance efficacy and tolerability, as well as minimizing adverse effects in the short and long term.

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