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THE KETOGENIC DIET VS. CIVILIZATIONAL DISEASES: A REVIEW OF ITS APPLICATIONS IN DIABETES, ALZHEIMER'S DISEASE, AND ONCOLOGY

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ABSTRACT

The ketogenic diet (KD) - a high-fat, low-carbohydrate, and moderate-protein diet - is gaining increasing recognition as a potential strategy to help treat a variety of conditions, including cancer, type 2 diabetes, and neurodegenerative diseases such as Alzheimer's. KD's mechanisms of action are mainly based on inducing a state of ketosis, in which the body switches from using glucose to ketone bodies as its main energy source. Cancer remains one of the world's most serious public health problems, and the effectiveness of current anti-cancer therapies is still sometimes limited. As a result, there is a growing interest in methods that support treatment, including nutritional interventions. The ketogenic diet (KD), based on high-fat intake, low carbohydrate intake, and moderate protein intake, shows potential as an adjuvant therapeutic strategy for cancer treatment. KD can affect the metabolism of cancer cells by increasing oxidative stress and reducing glucose availability, making cancer cells more susceptible to chemotherapy and radiotherapy, while protecting healthy cells. The ketogenic diet has been used with great success for more than 100 years to alleviate the course of many serious neurological diseases. The rapidly increasing number of patients suffering from obesity and type 2 diabetes in recent years has forced the search for new, effective ways to reduce body weight. The use of the ketogenic or low-carbohydrate diet in this context is of increasing interest to both physicians and the general public. This review presents current evidence from preclinical and clinical studies on the anticancer properties of the ketogenic diet, including its effects on tumor growth, angiogenesis, immune response, and the inflammatory environment. In addition, the use of KD in the treatment of other conditions, such as diabetes and Alzheimer's disease, is discussed. Although the diet is widely used clinically and has shown promising results in treating many pathologies, further research is needed on its long-term safety, especially in the context of cardiovascular risk. The article also provides an overview of the mechanisms of action of KD and possible side effects resulting from its use.

KEYWORDS

Ketogenic Diet, Diabetes, Alzheimer's Disease, Cancers

CITATION

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Introduction.

The ketogenic diet has been gaining popularity in recent years. In 2020, it was the most searched diet in the United States, with 25.4 million unique queries on Google. The increase in this interest has led to the rapid growth of the keto diet food industry, leading to a valuation of the global ketogenic diet market at $9.57 billion in 2019 [1]. The diet's history dates back to ancient times, when fasting was used to treat epilepsy [2]. Its therapeutic effect was first mentioned in 1797, when it was noted that it could help diabetics. At the time, the diet included ingredients such as milk, lime water, bread, butter, pudding, meat, and rendered fat [3]. In 1911, the first modern cases of treating epilepsy with starvation were reported, when two doctors in Paris found that epileptic seizures were less severe while fasting [1]. In 1921, R. T. Woodyatt described that there is an increase in the level of ketone bodies during a high-fat diet and fasting. Based on this, Russell Morse Wilder introduced the term "ketogenic diet," defining it as a high-fat diet (60-75% fat, 15-30% protein and 10% carbohydrates), ako a method of treating epilepsy by increasing the level of ketone bodies, which have anticonvulsant effects [3]. The ketogenic diet has gained particular recognition in the treatment of epilepsy in children [1]. It was noted in ancient times that prolonged fasting could reduce the frequency of epileptic seizures. Pediatrician Mynie Gustav Peterman suggested introducing this diet in children, suggesting 1 gram of protein for every kilogram of body weight and limiting carbohydrates to 10-15 grams per day. This proved to be very effective, as in 1925 Peterman reported that in 95% of the 37 patients the number of seizures was reduced, and in 60% of them the seizures stopped completely. Over the following years, data were collected on the effects of the diet on about 100 patients, noting improvements in concentration, behavior, and sleep quality. Unfortunately, the diet also caused side effects, such as nausea and vomiting, associated with excessive ketosis, which led to the development of antiepileptic drugs in the 1940s and the decline in popularity of ketogenic therapy [3]. Despite its use until the 1930s, when the discovery of diphenylhydantoin, the first effective epilepsy drug, limited its use, the ketogenic diet began to be used again to treat difficult cases of epilepsy and other neurological diseases from the 1990s onward. Some studies have reported a decrease in the number of epileptic seizures by up to 24% in people on the ketogenic diet [3].

Materials and Methods

A comprehensive review of articles published in scientific journals was conducted using online research platforms such as PubMed and Google Scholar. Articles were identified using the following search terms: „Ketogenic diet"; „Diabetes"; „Alzheimer's disease"; „Cancers".

Discussion

The ketogenic diet is a diet characterized by high fat and limited carbohydrates, while adjusting protein and calorie levels [4]. The key principle of the ketogenic diet is to minimize carbohydrate intake, while maintaining appropriate proportions of protein and fat [1]. The classic version of the ketogenic diet, known as the 4:1 formula, means that fat accounts for 90% of calories, protein 8%, and carbohydrates only 2% of the total energy value [4]. For a person whose daily caloric requirement is 2,000 kcal, the daily amount of carbohydrates should not exceed 50 grams, but initially it is recommended to limit this amount to 20 grams per day [2]. On a ketogenic diet, foods such as cereals, potatoes, rice, fruits, starchy vegetables, and legumes are replaced with foods rich in fat and protein, mainly of animal origin [5]. Typical dietary ingredients include eggs, meat, fatty fish, vegetable oils (e.g., olive oil and coconut oil), offal (e.g. liver, heart, kidney), non-starchy vegetables (especially greens such as broccoli, spinach, arugula, kale), avocados, olives, and nuts [6]. The goal of the ketogenic diet is to induce ketosis, a metabolic process in which the body switches from using glucose

to burning fatty acids, leading to the production of ketone bodies, such as acetoacetate and β-hydroxybutyrate, which provide an alternative energy source [7]. It is believed that ketosis promotes weight loss and can have a positive effect on health by reducing blood glucose levels and improving lipid profiles [1]. The most common form of ketogenic diet is one based on long-chain triglycerides (LCTs), but due to its high fat content (about 90%) and significant change in previous eating habits, it is difficult to maintain over the long term. Therefore, to facilitate the body's adaptation, a diet using medium-chain triglycerides (MCTs) is often recommended [8]. In recent years, alternative ketogenic diet protocols have been developed to make it easier to follow. In addition, in addition to macronutrient ratios, other aspects, such as fatty acid composition and nutrient density, that affect the long-term efficacy and adherence of the ketogenic diet are increasingly being considered [4].

Modifications of the ketogenic diet

As an alternative to the traditional ketogenic diet, there are various modifications of it, such as the medium-chain triglyceride (MCT) diet or the Atkins diet. Developed in the 1970s by Dr. Robert Atkins, the Atkins diet focuses on limiting carbohydrates and increasing fat intake, but unlike the classic ketogenic diet, it does not place restrictions on protein or calories [4]. In contrast, the high-protein ketogenic diet (MAD), which is a modified version of the Atkins diet, aims to maintain a state of ketosis, limiting carbohydrate intake to 10-20 grams per day for both children and adults. In this version of the diet, protein accounts for 27%, carbohydrates for 39%, and fats for 34% of total caloric intake [8]. The main difference between the Atkins diet and MAD is the stricter restriction of carbohydrates in MAD and the greater emphasis on fat, with the goal of this diet not being direct weight loss [4]. Research by Murray and colleagues indicates that MAD can support cognitive function and help treat some neurological disorders [8]. In 2012, a review was published on the use of MAD in the treatment of epilepsy, which concluded that this diet can effectively control seizures and should be the first treatment option in this patient group [4]. A diet based on medium-chain triglycerides (MCTs) differs from the classic ketogenic diet because it contains fatty acids, such as octanoic and decanoic acid, which are rapidly absorbed and converted to ketone bodies in the liver. Due to their faster absorption and metabolism, MCTs are a more efficient source of energy than long-chain fatty acids, which require more complex processing [8]. Another option is the very low calorie ketogenic diet (VLCKD), in which daily carbohydrate intake ranges from 20 to 50 grams, and can be less than 10% of daily caloric intake at 2,000 kcal for more physically active individuals [2]. Regardless of whether VLCKD includes plant or animal products, the main idea is to significantly reduce carbohydrate intake and protein, which in most cases should not exceed 1 g per kilogram of body weight [3]. Low glycemic index treatment (LGIT) is another alternative, in which high glycemic index (GI) foods are replaced with low GI ones. Although this diet does not lead to continuous ketosis, it positively affects carbohydrate metabolism and is easier to follow. The cyclic ketogenic diet (CKD) combines periods of a ketogenic diet with a high-carbohydrate diet to replenish muscle glycogen stores [2].

Physiological ketosis

Under standard conditions, the body mainly uses carbohydrates for energy, and insulin plays a key role in storing energy from glucose. When carbohydrate intake is restricted, the body's insulin levels drop [1]. Reducing the amount of carbohydrates in the diet leads to a change in metabolism, causing what is known as “physiological ketosis,” which is different from the pathological ketoacidosis seen in diabetes. After a few days of starvation or eating a diet with very low carbohydrates (less than 20 grams per day), the body's glucose stores become insufficient to maintain oxaloacetate production and support fat oxidation processes in the Krebs cycle. Since the only source of energy for the central nervous system is glucose, and fatty acids do not pass through the blood-brain barrier, the body must find an alternative source of energy [3]. In this situation, fat stores are used. Free fatty acids (FFAs) released from adipose tissue go to the liver, where they undergo ß-oxidation in the mitochondria to form acetoacetyl-CoA, which is converted into ketone bodies (CTs) [3]. The three main ketone bodies are acetoacetate (AcAc), β-hydroxybutyrate (BHB), and acetone. Acetone is formed spontaneously and is exhaled through the lungs or can be further metabolized to pyruvate, lactate, and acetate [4]. In ketogenic diet therapy, β-hydroxybutyrate plays a major therapeutic role with pleiotropic properties [3]. The main sources of ketone bodies are fatty acids, although a small amount of ketones can also come from leucine, phenylalanine, and tyrosine metabolism [4]. An increase in the level of ketone bodies in the body and their excretion in the urine leads to the appearance of ketonemia and ketonuria. Under physiological conditions, the concentration of ketone bodies in the blood is very low (<0.3 mmol/L), but when their level rises above 4 mmol/L, they become an important source of energy for the brain. In diabetic ketoacidosis, the concentration of ketone bodies can rise to 25 mmol/l, which is associated with a lack of insulin, high glucose levels (>300

mg/dl), and reduced blood pH (below 7.3) [7]. The production of ketone bodies occurs mainly during starvation and prolonged exercise, but can also occur when following a very low-carbohydrate diet [1]. After three days of starvation, ketone bodies provide 30-40% of total energy. Their levels rise especially in the first 10 days of starvation, and reach a plateau after about 30 days. In particular, the heart, skeletal muscles, kidneys, and brain begin to use ketone bodies. During a starvation or ketogenic diet, when glucose levels are low, the brain can derive 60-70% of its energy from ketones. Although the liver produces ketone bodies, it can't use them in large quantities because it doesn't have the enzyme to use them efficiently. The process of switching from glucose to ketones and fatty acids as the main sources of energy can take up to a week. Ketone bodies play an important energy role, especially during periods of starvation and during early brain development in children [4].

The use of the ketogenic diet

Cancer represents one of the greatest public health challenges worldwide, and despite numerous advances in treatment, there is still a lack of effective approaches to support traditional cancer therapies. A ketogenic diet, rich in fat and low in carbohydrates, with adequate protein, shows potential in improving the effectiveness of standard cancer treatment. By affecting the metabolism of cancer cells, the diet can make tumors more amenable to drug treatment. Studies indicate that a ketogenic diet can reduce tumor growth, protect healthy cells from the effects of chemotherapy and radiation therapy, increase drug toxicity to cancer cells, and reduce inflammation. In addition, the ketogenic diet is a cheaper and easier-to-implement therapeutic option compared to traditional therapies. There is also evidence that the ketogenic diet can be effective in the treatment of obesity, diabetes, polycystic ovary syndrome, acne, and neurological diseases such as Alzheimer's and Parkinson's [4]. Over the past few decades, since the 1970s, the number of people suffering from obesity has tripled worldwide. According to projections, by 2030, about 38% of adults will be overweight and 20% will face obesity. This phenomenon goes hand in hand with the rising incidence of chronic conditions such as type 2 diabetes and cardiovascular disease, which are often linked to obesity and poor lifestyle [9]. In Europe, obesity affects between 10% and 25% of men and women. Studies note that obesity worsens glucose metabolism, leads to insulin resistance, and damages pancreatic beta cells. One of the main factors contributing to this problem is physical inactivity and an unhealthy diet. Calorie reduction has been shown to reduce the incidence of obesity-related diseases, such as type 2 diabetes, while bringing positive health effects, including reduced inflammation. For this reason, a low-calorie diet is considered an effective method to promote weight loss and improve health in people with obesity and diabetes [10]. Ketone molecules produced in the body during a ketogenic diet exhibit an appetite suppressant effect, activating relevant areas in the brain responsible for controlling appetite. Combining this effect with the satiety-promoting properties of proteins makes the ketogenic diet more effective at regulating feelings of hunger, making it easier to follow [11]. The diet increases feelings of satiety and reduces appetite by increasing levels of hunger-inhibiting hormones such as glucagon-like peptide 1, leptin, and cholecystokinin, while decreasing levels of ghrelin, an appetite-stimulating hormone [5]. In 2019, the American Diabetes Association (ADA) approved a low-carbohydrate diet as a treatment for type 2 diabetes, with studies showing that the diet is effective in improving blood glucose control by inducing a state of nutritional ketosis, which can lead to reduced reliance on diabetes medications. However, the ADA noted the need for an individualized approach to diet planning, taking into account patients' dietary preferences and metabolic goals, as such a diet is associated with certain difficulties [9]. This review outlines the mechanisms of action of the ketogenic diet in the treatment of neurodegenerative diseases, cancer, and diabetes, based on the available evidence [8].

Ketogenic diet in cancer treatment

It is well known that diet plays an important supporting role in the treatment of oncological diseases, so high hopes are placed on the development of diets as a possible adjuvant to cancer treatment. One of the most universal metabolic changes, i.e., oxidative stress, causes cellular damage by excess reactive oxygen species (ROS), leading to cancer cell death [12]. Increased glucose consumption helps cancer cells maintain redox balance by neutralizing reactive oxygen species (ROS), such as hydrogen peroxide (H2O2) and superoxide anion radical (O2--), which are formed by abnormal mitochondrial metabolism [13]. Therefore, high-fat, low-carbohydrate ketogenic diets (KD) that enhance mitochondrial oxidative metabolism while limiting glucose consumption could represent an easy and effective approach to selectively enhance metabolic stress in cancer cells versus normal cells. Recently, several studies have shown the impact of the ketogenic diet as an adjuvant to cancer therapy in both animal models and human case reports. Glioblastoma multiforme (GBM) is the most common type of highly aggressive brain tumor among elderly people with an extremely poor prognosis.

Danielle M Lussier et. al have shown the role of a therapeutic ketogenic diet in enhancing immunity in a mouse model of malignant glioma. The aim of this study explain the suppression of proinflammatory microenvironment conditions and enhance the activity and number of CD8+ T cells, making them more effective in recognizing and destroying tumor cells [14]. Another reported study by Woolf EC et al. describes some of the effects observed in a mouse model of malignant glioma using the ketogenic diet. The diet consisted of approximately 72% energy from fat, 3% from carbohydrate, and 5% from protein. A reduction in the protein expression of VEGFR2, the main receptor responsible for modulating tumour angiogenesis, was observed, leading to a reduction in the number of vessels feeding the tumor. The diet also reduced the expression of several other proteins that modify the tumor microenvironment during hypoxia, the trigger for angiogenesis [15]. The literature describes the case of a 65-year-old woman with a partial tumor of a highly invasive GBM resection, and next used the ketogenic diet administered in restricted amounts (R-KD). A restricted diet included a 4:1 (fat: carbohydrate + protein) ketogenic diet, which provided about 600 kcal per day. After 14 days of the R-KD initiation of standard therapy (radiation with temozolomide chemotherapy). No tumour growth was observed for 8 months after starting the ketogenic diet, which was considered evidence of disease stabilisation. [16] Pancreatic cancer also with a bad prognosis. Amir Zahra et.al conducted a study on a pancreatic cancer xenograft model to test the hypothesis that the ketogenic diet, along with radiation or chemotherapy, may help to alter the metabolism of cancer cells and improve therapeutic outcomes. The KD contained a 4:1 ratio of fat grams to grams of protein + carbohydrate (90% of calories from fat, 8% from protein, 2% from carbohydrate). Mice treated with KD and radiation survived significantly longer and had a slower tumor growth rate than mice treated with radiation alone. [17] In addition, Mavropoulos *et al*. showed that a very high-fat/no-carbohydrate ketogenic diet (NCKD: 83% fat, 0% carbohydrate, 17% protein) significantly reduced median serum systemic factors such as insulin, IGF-1(Insulin-like growth factor 1), which is a known mitogen to prostate cancer cells. The Akt pathway associated with inflammatory cytokines, which could modulate tumor growth and survival progression, was also significantly reduced in NCKD relative to MCD (high-fat/moderate-carbohydrate diet (MCD: 40% fat, 43% carbohydrate, 17% protein) tumor. [18] In one study result revealed that KD with different kinds of fatty acids enhanced survival and slowed tumor growth in mice with colon cancer, Hao *et al*. divided animals into three feeding groups: a KD rich in omega 3 fatty acids and medium-chain triglycerides (MCT) (MKD group), lard only (LKD group) and standard diet (SD) group for 45 days. LKD and MKD significantly increase survival time and can inhibit the growth of tumors of the human colon cancer cell line in a xenograft model. Furthermore, cancer patients with advanced, incurable cancer are typically threatened by cancer cachexia, which is characterised by a negative protein and energy balance. A non-restricted ketogenic diet may therefore be able to benefit cachectic cancer patients if supplemented with adequate lipids. The ketogenic diet (both MKD and LKD) described in this study induced a clear increase in body weight during the duration of the study. [19] It should be considered that all these preclinical trials have been carried out in individual cases, and differences in physiology between animals and humans require clinical trials in this area to be initiated to confirm their efficacy in patients with tumors.

Ketogenic diet in the treatment of diabetes

Since the 1970s, global obesity rates have tripled. Every year, there is a steady increase in the number of people struggling with the problem, and forecasts predict that by 2030, some 38% of the world's adults will be overweight, and 20% will be obese. The incidence of chronic conditions such as type 2 diabetes and cardiovascular disease is rising as life expectancy increases. In addition, these diseases are strongly associated with excessive nutrient intake and obesity [20]. Today, obesity affects 10% to 20% of men and 10% to 25% of women in European countries. Many studies refer to the impact of obesity on glucose metabolism, deterioration of glucose tolerance, development of insulin resistance, and damage to pancreatic islet B-cell function. One key contributing factor to obesity is reduced physical activity levels and an inadequate diet. Studies show that calorie reduction reduces or slows obesity-related diseases, such as type 2 diabetes, resulting in significant weight loss and positive anti-inflammatory effects. In this context, a low-calorie diet may be an effective therapeutic strategy to promote weight loss in people with obesity, diabetes, and pre-diabetes. In recent years, several studies have been conducted to analyze dietary interventions, including the ketogenic diet and the very-low-calorie ketogenic diet, as therapeutic dietary approaches for treating diabetes and obesity [21]. Originally developed to treat epilepsy, the ketogenic diet has shown significant therapeutic effects [22]. It has been shown to reduce seizure frequency in patients with refractory epilepsy, and some patients have even achieved complete and permanent remission [20].

Type 1 diabetes

Type 1 diabetes (T1D) accounts for 5-10% of all cases. In this disease, the immune system attacks the beta cells of the pancreas, which are responsible for producing insulin. Insulin is a key hormone that allows glucose to be transported from the blood to the cells, where it is used as an energy source. Due to the lack of sufficient insulin, the transport of glucose into cells is impaired and manifests as elevated serum glucose levels [4]. Historically, the use of ketogenic diets in the treatment of type 1 diabetes dates back to the early 20th century. The first study that detailed the use of a ketogenic diet in this disease was published by Henwood and colleagues in 2006. In contrast, for type 2 diabetes, there is evidence of the use of the ketogenic diet as early as 1914-1922 [4]. The ketogenic diet may affect insulin requirements in patients with type 1 diabetes. Reducing carbohydrate supply leads to smaller fluctuations in blood glucose levels, which may result in lower insulin requirements. A study found that some patients following this diet experienced significant reductions in insulin doses (by 44.3%), which is particularly important for those using insulin pumps [4]. The ketogenic diet may have an impact on type 1 diabetes, particularly in the context of autoimmunity, which leads to the destruction of pancreatic beta cells. Disturbances in intestinal homeostasis, including a reduction in butyrate-producing intestinal bacteria, may contribute to this process. A protective effect of butyrate on the process of pancreatic cell autoimmunity has been suggested. During a ketogenic diet, there is an increase in the concentration of β-hydroxybutyrate, which is the main ketone body. In addition, β-hydroxybutyrate has been shown to have an inhibitory effect on inflammatory processes and Th17 cell activity. Which can be used to protect pancreatic β-cells [4]. Although ketogenic diets can improve glycemic control in children with type 1 diabetes, they are usually not recommended in this group of patients because of the risk of malnutrition, stunted growth, impaired bone density, hyperlipidemia, sleep disorders, amenorrhea, and hypoglycemia [22]. Adequate diet and regulation of insulin supply play a key role in the treatment of type 1 diabetes. In recent years, more and more attention has been paid to the use of low-carbohydrate diets, including the ketogenic diet, as potential tools to help treat the disease. One study was conducted on a group of 22 adults with type 1 diabetes who chose to follow a ketogenic diet or a very low-carbohydrate diet containing 70-90 grams of carbohydrates per day. The duration of follow-up was 12 months, and the study aimed to evaluate the effect of this diet on the participants' glycemic control, insulin requirements, and lipid profile. The ultimate goal of diabetes treatment is to minimize the risk of hypoglycemia, which poses a serious threat to patients' health. A significant reduction in the number of hypoglycemic episodes was observed in the study group. This is an important result that suggests that the ketogenic diet can help stabilize blood glucose levels and reduce the glycemic fluctuations that are common in patients with type 1 diabetes. Over the 12 months of the study, participants showed an average reduction in glycated hemoglobin levels from 7.5% to 6.4%. The study group showed an almost 50% decrease in postprandial insulin requirements, from 21.1 IU per day to 12.4 IU per day. This is a significant change, suggesting that a low-carbohydrate diet can improve insulin sensitivity and reduce the need for insulin administration. Reducing the need for insulin may also help reduce the risk of hypoglycemia and other complications associated with excessive insulin use. Analysis of blood lipid levels showed that total cholesterol and HDL cholesterol values did not change significantly after 12 months on the ketogenic diet. The value of HDL cholesterol, considered the "good" cholesterol, remained stable, which is beneficial from the point of view of cardiovascular health. Triglyceride levels, on the other hand, decreased by an average of 16%, a favorable result since high triglyceride levels can be a risk factor for heart disease [4].

Type 2 diabetes

Type 2 diabetes (T2D) is a serious health problem whose incidence is increasing worldwide. It is the most common form of diabetes, accounting for more than 90% of all diagnosed cases. Its etiology is complex, involving insulin resistance and insufficient insulin secretion. In 2017, the global prevalence of T2D was estimated at 462 million people. The number of people with T2D is projected to rise to 552 million by 2030, indicating the need for effective prevention and treatment strategies [23]. Patients with type 2 diabetes are at higher risk of developing cardiovascular disease, diabetic neuropathy, and other complications, which are the leading causes of death associated with the disease [24]. Focusing on preventing complications and optimizing patients' quality of life is key. Blood glucose control, management of cardiovascular risk factors, and weight reduction are essential components of treatment. Guidelines from the American Diabetes Association and the European Association for the Study of Diabetes place a strong emphasis on lifestyle interventions, such as dietary changes and increased physical activity, which should be the first therapeutic component. These interventions are also recommended as adjunctive therapy for those already taking diabetes medications. Unfortunately, many patients have difficulty adhering to therapeutic recommendations, leading to poor

glycemic control and a higher risk of cardiovascular complications [23]. The main goal of type 2 diabetes treatment is to keep glycated hemoglobin (HbA1c) below 7% (53 mmol/mol). A diet rich in vegetables, fruits, whole grains, fish, nuts, and legumes is recommended, along with a limited intake of processed meat, refined carbohydrates, and artificially sweetened beverages. The goal is to achieve a weight reduction of at least 15 kg, which is associated with improved glycemic control. Nonetheless, lifestyle interventions often have only short-lived effects, resulting in moderate weight loss (about 5%), which is usually not enough to significantly improve glycemic levels, especially in the context of achieving diabetes remission. The goal is to achieve a weight reduction of at least 15 kg, which is associated with improved glycemic control. Nonetheless, lifestyle interventions often have only short-lived effects, resulting in moderate weight loss (about 5%), which is usually not sufficient to significantly improve glycemic levels, especially in the context of achieving diabetes remission [6]. The first large study describing the use of a strictly ketogenic diet in patients with type 2 diabetes was published in 1996 [4]. In type 2 diabetes, the ketogenic diet is much more popular compared to type 1 diabetes. A comprehensive meta-analysis of randomized controlled trials showed that the ketogenic diet was more effective than a low-fat diet in improving glycemic parameters, body weight, and lipid profile. The meta-analysis looked at the effects of the ketogenic diet on glycemic control, insulin resistance, and lipid metabolism in patients with type 2 diabetes. Glucose levels, glycated hemoglobin (HbA1c), lipid profile (total cholesterol, LDL, HDL, triglycerides), and body mass indices (weight, waist circumference, BMI) were studied. As a result of the ketogenic diet, an average reduction in glucose levels of 1.29 mmol/L was observed. In addition, glycated hemoglobin (HbA1c) levels decreased by an average of 1.07%. The ketogenic diet also showed positive effects on lipid metabolism. A reduction in the levels of total cholesterol, LDL fraction, and triglycerides was observed. At the same time, the concentration of HDL cholesterol increased. These changes are beneficial from the point of view of cardiovascular health since lowering LDL and triglyceride levels while increasing HDL may reduce the risk of heart disease, which is a common complication of type 2 diabetes. Another important outcome of the ketogenic diet was weight loss. The average weight loss was 8.66 kilograms, a significant improvement, considering that overweight and obesity are risk factors for the development of type 2 diabetes and other comorbidities, such as hypertension and dyslipidemia. In addition, a reduction in waist circumference by an average of 9.17 cm and a decrease in body mass index (BMI) by 3.13 kg/m² were observed [4]. Another study selected 83 obese patients (39 men and 44 women) with a body mass index greater than 35 kg/m2 and high glucose and cholesterol levels. A 24-week follow-up was conducted. The ketogenic diet reduced the patient's weight and BMI and significantly improved glycemic and lipid profiles (lowering blood glucose, triglycerides, and LDL cholesterol) and increasing HDL cholesterol [20,25]. The ketogenic diet was also associated with a significant reduction in waist circumference and abdominal obesity, which are key risk factors for the development of diabetes and its complications [24]. The ketogenic diet results in a significant reduction in the need for insulin or antidiabetic drugs and, in some cases, their complete withdrawal. Therefore, patients taking insulin or oral medications should be carefully monitored [26]. In contrast, those taking SGLT2 inhibitors or GLP-1 receptor agonists should discontinue their use before starting a ketogenic diet due to the risk of ketoacidosis and hypoglycemia. In the case of metformin, there are no clear contraindications, but each situation should be considered individually. It is worth mentioning that the ketogenic diet can lead to a reduction or complete cessation of pharmacotherapy, and in some cases, to remission of type 2 diabetes [4].

Ketogenic diet for the treatment of Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia, affecting some 50 million people worldwide. It is a complex disorder that leads to gradual cognitive impairment, including memory loss, confusion, self-care problems, and a changing personality. At the onset of the disease, short-term memory problems are most common, affecting patients' daily lives [7]. The increased risk of Alzheimer's disease is age-related, and experts predict that the number of cases of the disease will increase in the future [2]. It is important to identify risk factors, such as age, head injuries, vascular problems in the brain, smoking, and depression, which can accelerate the development of the disease. In addition, genetic factors have a significant impact on the progression of AD [2]. At the pathological level, AD is characterized by the accumulation of β-amyloid peptide (Aβ) in the form of amyloid plaques, the presence of neurofibrillary tangles (NFTs) as a result of hyperphosphorylation of tau protein, and loss of neurons in the hippocampus [7]. Amyloid deposition can begin up to 20 years before the onset of clinical symptoms [2]. In addition, patients with Alzheimer's disease exhibit mitochondrial dysfunction and glucose hypometabolism in the brain [7]. The associated high-glycemic diets can lead to insulin resistance, which increases the risk of developing the disease [2]. There is evidence

that high glycemic index diets accelerate amyloid deposition in both mice and humans [7]. Glucose hypometabolism in the brain is a significant risk factor for the future development of dementia [2]. Currently, there are only a few FDA-approved drugs available, such as acetylcholinesterase inhibitors and memantine, which improve neurotransmitter function and alleviate behavioral symptoms, but do not prevent disease progression. In the absence of effective therapies, the potential benefits of dietary and metabolic interventions to affect the course of the disease are increasingly being highlighted [7]. Current treatment approaches are mainly based on slowing the progression of symptoms. Alzheimer's disease can be treated with pharmacological and non-pharmacological therapies, such as cognitive exercise, physical activity, and an appropriate diet. The Mediterranean diet, particularly extra-virgin olive oil (EVOO), is one approach that is gaining popularity [2]. The ketogenic diet, which produces ketones, may have a protective effect on brain cells, especially in the aging process. Ketones can support mitochondrial function, reduce inflammation, and reduce the expression of apoptotic mediators, making the ketogenic diet a potential treatment option for neurodegenerative diseases, including Alzheimer's [7]. This diet can help improve glucose metabolism in the brain by providing an alternative energy source in the form of ketones. In addition, the ketogenic diet may reduce amyloid accumulation by reducing β-amyloid (Aβ) toxicity [2]. Numerous preclinical studies indicate that the ketogenic diet can effectively promote the treatment of Alzheimer's disease. Improved memory function and decreased levels of amyloid and phosphorylated tau have been observed in mice following this diet. Preliminary clinical studies also suggest the benefits of ketogenic therapy in Alzheimer's patients, improving both blood ketone levels and cognitive function. A study of 20 Alzheimer's patients treated with MCT (medium-chain triglycerides) beverages or placebo showed a significant increase in β-hydroxybutyrate levels and improved cognitive function in those taking MCTs [8]. Studies on patients with Alzheimer's disease have shown that the ketogenic diet normalizes glucose metabolism in the brain, reduces insulin levels, and improves insulin sensitivity, resulting in improved performance on cognitive tests and offering hope for its use in the treatment of neurodegenerative diseases [2]

Risks of the ketogenic diet

The ketogenic diet, despite its potential benefits, is associated with some negative side effects. Among the most common are dehydration, electrolyte disturbances, vitamin deficiencies, and reduced bone density, which increases the risk of osteoporosis [27]. Chronic ketoacidosis can decrease vitamin D activity, which reduces its conversion to its active form, thereby affecting bone health, which can lead to osteopenia and fractures, especially in the elderly and postmenopausal women [5]. This diet can also promote the formation of kidney stones and increased uric acid production. To reduce these effects, electrolyte, vitamin, and mineral supplements, and increased fiber and fluid intake are recommended, which can help prevent constipation [26]. Clinical studies show that maintaining a ketogenic diet can sometimes be difficult for patients. Problems with tolerance of the diet and lack of motivation can lead to its premature termination. The diet must be properly balanced to prevent deficiencies caused by the elimination of carbohydrate-rich foods and other important nutrients, such as thiamin, folic acid, vitamin A, vitamin E, vitamin B6, calcium, magnesium, iron and vitamin K. Patients on a ketogenic diet may experience a deficiency of fiber, which is crucial for the proper functioning of the digestive system. Its lack leads to problems with nutrient absorption, impaired production of hormones that control appetite, and weakened immunity. The most difficult stage is the introduction of the diet, when symptoms such as hypoglycemia, dehydration, and gastrointestinal distress are most common. In some cases, patients also experience constipation, irritability, or mood changes. Constipation can be relieved by increasing fiber, using enemas, or administering polyethylene glycol. The controversy surrounding the ketogenic diet often concerns its effect on the lipid profile. Increased fat intake leads to an increase in serum lipid fractions [2]. However, doctors' concerns about the possibility of worsening metabolic indices, especially cholesterol and triglycerides, are partially allayed by studies that show improvements in body composition and blood parameters. In a study on patients with type 2 diabetes who followed a ketogenic diet for 56 weeks, a significant reduction in body weight, body mass index, total cholesterol, LDL cholesterol, triglycerides, and blood glucose levels, and a significant improvement in HDL levels were noted [4].

Conclusions

The ketogenic diet is gaining popularity, both among those seeking effective treatments and those who want to improve their fitness and health. Beginning as a treatment for epilepsy, the diet has its roots in therapeutic fasting used since ancient times [2]. The first modern research on the ketogenic diet began in the 1920s, when R.T. Woodyatt and Russell Wilder introduced the term "ketogenic diet" and proved its effectiveness in treating epilepsy [3]. Over time, the diet became widely used, and its therapeutic effects began to extend to other neurological diseases [1]. The classic ketogenic diet is based on a very low-carbohydrate, high-fat fat and moderate-protein intake, leading to a state of ketosis in which the body switches to using fat as its main source of energy [4]. Reducing carbohydrate intake and increasing the proportion of fats, including medium-chain triglycerides (MCTs), improves the effectiveness of the diet, as well as facilitating its long-term use [8]. Modern modifications of the ketogenic diet, such as the Atkins diet or modified Atkins diet (MAD), are tailored to various therapeutic goals and can be effective not only in the treatment of epilepsy, but also in improving cognitive function and treating metabolic disorders [4,8]. In the context of cancer treatment, the ketogenic diet can increase the sensitivity of cancer cells to standard therapies, speeding up their effects, reducing inflammation, and protecting healthy cells from damage by chemotherapy or radiation therapy [8]. In addition, the ketogenic diet has shown potential in the treatment of obesity and type 2 diabetes, contributing to weight loss and improving metabolic parameters such as blood glucose and insulin levels [10]. For neurodegenerative diseases such as Alzheimer's disease, the ketogenic diet has neuroprotective effects. Increasing blood levels of ketones can support mitochondrial function and reduce amyloid peptide deposition in the brain, which promotes improved cognitive function [2,7]. In clinical studies, improvements in cognitive test scores have been observed in people with Alzheimer's disease following a ketogenic diet [8]. The ketogenic diet is also increasingly recognized as effective in the treatment of type 2 diabetes, where it helps control blood glucose levels and reduces insulin requirements [4, 23]. In type 1 diabetes, its use can lead to a reduction in insulin requirements, with promising results, especially in terms of a lower risk of hypoglycemia [4]. However, the ketogenic diet is associated with certain risks and side effects. These include dehydration, electrolyte disturbances, vitamin deficiencies, and the risk of osteoporosis, especially in the elderly [13]. In addition, it can lead to gastrointestinal problems, such as constipation, and alter the lipid profile, raising concerns about its long-term use [2]. In conclusion, the ketogenic diet is a promising adjunctive treatment for many metabolic and neurodegenerative diseases. Nevertheless, its use should be monitored to avoid potential side effects and to ensure its effectiveness in long-term treatment [10].

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