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EC NUTRITION
Review Article

Beyond Weight Loss: A Comprehensive and Concise Review of the Ketogenic (Keto) Diet from Epilepsy Origins to Weight Management

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Received: November 24, 2022; **Published:** February 28, 2023

DOI: 10.31080/ecnu.2023.18.01087

Abstract

The ketogenic diet (KD) is a high-fat, adequate-protein, and very low-carbohydrate diet that stimulates the creation of ketones by mimicking the metabolism of the fasting state. A high level of blood ketone caused by a KD induces the state of ketosis, which has several physiological and therapeutic advantages. The KD first gained popularity as an epilepsy treatment in the 1920s and 1930s. It has rapidly attracted research interest in the last 20 years due to mounting evidence of the KD's possible therapeutic potential for other diseases besides epilepsy, including obesity, neurodegenerative diseases, and malignancies.

The KD alters multiple cellular signaling cascades, receptors, and biomarker levels in various medical situations. KD therapy differs from the typical Western diet in that it focuses on nutritional supplements, electrolytes, and hydration in addition to the diet. If the KD is followed closely, significant dietary changes can positively affect the dieting individual. However, several treatable short- and long-term adverse effects are linked to the KD. It may be challenging to follow the KD long-term if some of the most enjoyable meals are not allowed.

Numerous physicians are considering including KD programs in the therapeutic regimen in light of the importance of lifestyle modification in managing diseases. However, before this can be advised, doctors must ensure its efficacy and safety, and further human research is necessary. Numerous economic opportunities will soon arise as a result of the potential medical benefits of the KD. These safeguards and limitations can therefore be used to develop distinctive and personalized interventional procedures replicating the effects of a KD or as potential drug development targets.

Keywords: *Epilepsy Treatment; High-Fat; Low-Carbohydrate Diet; Elevated Ketone Level; Neurodegenerative Disease; Obesity*

Abbreviations

KD: Ketogenic (Keto) Diet; LCD: Low-Carbohydrate Diet; LCHF: Low-Carb, High-Fat; PSMF: Protein-Sparing Modified Fast; SGLT2: Sodium-Glucose Cotransporter 2

Introduction

Since 500 BCE, fasting and diet regimens have been used to treat epilepsy. Consuming a modified diet consisting of high fat, moderate protein, and low carbs, the body shifted to fasting mode [1]. This low-carb diet forces the body to break fat into ketones, which are used as an energy source. In the 1920s and 1930s, the ketogenic diet (KD) became widespread as a therapy for epilepsy [2]. However, with the discovery of antiepileptic drugs, the use of this regimen decreased dramatically.

In 1921, Rollin Woodyatt, the famous endocrinologist, reported for the first time that the liver produced three water-soluble compounds, acetone, β-hydroxybutyrate and acetoacetate (together called ketone bodies) were produced by the liver as a result of starvation or with a diet rich in fat or low in carbohydrates [3]. This diet was later (in 1921) called the 'ketogenic diet' by Russel Wilder, who proposed that dieters could obtain the benefits of fasting if ketonemia were produced by other means [1].

Peterman from the Mayo Clinic reported on the calculation of a KD. This calculation consists of 1g of protein per kilogram of body weight in children, 10 - 15g of carbohydrates per day, and the remaining calories from fat [4]. A KD has evolved to primarily consist of low carbohydrates, moderate proteins, and high fats. The dietary macronutrients are divided into approximately 5% to 10% carbohydrates, 30% to 35% protein, and 55% to 60% fat to precisely deliver a 2000 kcal per day diet. Many studies also described the different KD regimens.

Accordingly, to date, there are four significant types of the KD with proven efficacy: a) classic long-chain triglyceride KD, b) medium-chain triglyceride KD, c) modified Atkins diet, and d) treatment with low glycemic index [5]. Many researchers believe that diseases enter the body through the mouth. Consequently, a restricted diet can be advocated to improve health [6].

In line with this premise, two eating plans—the typical KD and therapeutic KD—are being investigated that place various restrictions on carbohydrate consumption for their potential effects on health [7].

Since 1920, several studies have reported the beneficial role of the KD in improving behavior and exerting cognitive benefits. The KD has recently experienced a reemergence, and modern clinical studies have established the treatment as significantly effective [8].

The KD is now available in more than 45 countries [9]. According to Wheless (2008), the KD "was revealed that the KD was the next-to-the-last or last choice for treatment of almost all childhood epilepsies" [10].

Although the KD has become a fad among fitness and weight-loss enthusiasts, it was initially developed for medical and therapeutic applications [5]. However, over time, the KD has proved beneficial in pediatric epilepsy management, managing or addressing metabolic disorders, specific weight management, congenital metabolic diseases, prevention or control of neurodegenerative disorders, and management of depression and anxiety.

The KD in human disorders and diseases

The KD has increasingly garnered research attention in the past decade, due to emerging evidence of the therapeutic potential for various diseases, in addition to epilepsy, from obesity to malignancies. Several reports proposed that the KD has probable beneficial results

in combating multiple neurological disorders, e.g., epilepsy, dementia, ALS, traumatic brain injury, acne, cancers, and metabolic disorders [5,7,9,10].

Chronic disease conditions

KDs can temporarily help some chronic conditions improve and control their symptoms [11]. However, these diets impact the quality of the diet, usually increasing the intake of foods associated with a higher risk of developing chronic diseases while reducing the intake of foods identified as protective in epidemiological research.

Neurologic conditions and cognitive disorders

AD is associated with neurodegeneration and the inability to utilize glucose by spared neurons efficiently. This association prompted using ketones as an alternative fuel source for these individuals [12]. In addition, short-term clinical trials showed that a diet with medium-chain triglycerides improved some measures of cognitive function in AD [13-15].

Inflammation and related disorders

The KD's effect on systemic inflammation are related to three main drivers: a) insulin reduction, b) BHB synthesis, and c) an increase in glucagon [16-18]. By regulating the balance between pro-inflammatory and anti-inflammatory cytokines. The KD is effective in symptomatic relief from inflammatory conditions, e.g., rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis [16]. The KD also effectively manages inflammatory bowel diseases and irritable bowel disorders [17]. The KD also reverses and controls neuroinflammation [18].

Prevention and management of diabetes

The KD improves glycemic control in patients with DM2 by reducing glucose uptake and improving systemic insulin sensitivity. Carbohydrate restriction by adapting to a KD significantly reduces postprandial and general glucose concentrations and HbA1c in diabetic patients [19,20]. In addition to glucose metabolism, the KD decreased the homeostatic model assessment of insulin resistance in patients with T2DM [21]. However, caution should be exercised when prescribing the KD to T2DM patients on other drug treatments, e.g., sodium-glucose cotransporter 2 (SGLT2) inhibitors (pro-ketogenic), insulin, and insulin secretagogues [22].

In adults with type 1 diabetes, favorable and unfavorable outcomes have been observed. The KD is generally not used in this population due to the risk of malnutrition, failure to thrive, reduced bone density, hyperlipidemia, poor sleep, amenorrhea, and hypoglycemia. In addition, mood and behavior can be adversely affected [23].

Obesity and weight management

In a long-term study by Dashti., *et al.* (2004), the KD significantly decreased BMI, blood cholesterol, and plasma glucose and increased weight loss, thus reducing risk factors for various chronic diseases associated with obesity in obese hypercholesterolemic patients with BMI > 35 kg/m^2 without any side effects [24].

A KD has a more beneficial effect on obesity than other diets. A meta-analysis of 11 studies reported significant weight reductions in the low-carbohydrate diets (LCDs) group compared to the low-fat diet group, attributed to lower energy intake rather than macronutrient composition [25]. Although there is limited information available, researchers have proposed several mechanisms for the effect of

the KD on weight loss. These effects are reduced appetite due to increased levels of satiety hormones, such as glucagon-like peptide-1, cholecystokinin, and ghrelin, regulation of satiety signaling; reduced lipogenesis and increased lipolysis; higher consumption of fats; and increased energy consumption due to increased gluconeogenesis [26-29].

Regulation of hypertension

A diet high in processed carbohydrates and refined sugars leads to arterial inflammation over time, which can cause an increase in blood pressure. Therefore, a diet low in carbs and sugars will decrease insulin levels and arterial inflammation [30]. Numerous studies suggest that a KD may help treat or prevent hypertension. For example, in a trial conducted on obese patients with hypertension, the KD was more effective in reducing blood pressure when combined orlistat with a low-fat diet therapy [31]. However, considering the significant data effect of the KD, it was not substantial in regulating blood pressure [32].

Controlling heart and cardiovascular disease

The cardiac muscle can use ketone bodies as a fuel source without FFA or glucose. Therefore, a KD is a more energy-efficient fuel and improves myocardial work efficiency and function [33]. The KD attenuates free radical-induced injury, improves heart energy reserves, increases myocardial acetyl-CoA content, and improves oxygen consumption transduction into efficiency at work at the mitochondrial level in the endangered myocardium and thus enhances myocardial metabolism [34].

Certain studies showed that the KD prevents ischemic tissue damage in animal models undergoing myocardial infarctions or stroke, leading to a significantly smaller area of ischemic and necrotic injury [35]. As the KD is characteristically high in fats, it is necessary to assess its potential effect on the lipid profile. Most animal studies used KDs rich in saturated fats, which may have detrimental effects on the lipid profile compared to a KD rich in unsaturated fats. Moreover, the KD has been associated with significant reductions in total cholesterol, triglycerides, and LDL and increases in HDL cholesterol levels [36].

Endocrine regulation and reproductive diseases

One of the most controversial topics surrounding the KD is its safety concerning hormones. Some say a KD is helpful for regulating hormones, and others say the opposite. Various hormones, e.g., insulin, glucagon, cortisol, catecholamines, and growth hormone, also significantly affect ketone-body metabolism. Implementing a KD regulates insulin and improves blood sugar control, leading to a healthier and more fulfilling life. Improvements in body weight evidence the endocrine effects of low-carbohydrate KD, free testosterone percentage, luteinizing hormone/follicle-stimulating hormone ratio, and fasting insulin levels. It leads to a decrease in androgen secretion and an increase in sex-hormone-binding globulin, improves insulin sensitivity, and thus renormalizes endocrine functions [37]. Such diet intervention and lifestyle management have beneficial effects in treating patients with PCOS affected with obesity and type 2 diabetes [38].

Anti-aging

The KD may have benefits in keeping humans healthier for longer. In mice, long-term exposure to a KD, fed every other week from middle age, reduces midlife mortality, extends longevity, and preserves motor function, muscle mass, and memory in aging [39]. Carbohydrate restriction with the KD can also induce metabolic switching that helps to prevent several metabolic, neurodegenerative, inflammatory, and malignancies associated with aging. However, clinical studies are lacking in this field [40].

Malignancies

Tumor cells use glycolysis glucose as the primary energy source in the presence of oxygen [41]. Thus, any pharmacological intervention that reduces intratumoral glucose levels may slow tumor growth. During the implementation of a KD, tumor cells have limited access to glucose. They cannot use ketone bodies as an energy source due to aberrant mitochondrial function and reduced enzymatic activity for ketone consumption, which makes the KD a possible approach for cancer prevention.

This occurrence concomitantly limits glucose-dependent signaling in tumor cells, and this glucose starvation inhibits neovascularization and angiogenesis and causes ultimate necrosis in tumor cells [42]. In addition to slowing tumor growth, a KD sensitizes tumor cells to traditional chemotherapy or radiotherapy in neuroblastoma, glioma, and lung cancer [43].

Ketogenic versus typical Western diets

The Standard American (Western) Diet was born out of convenience with the excessive amount of cheap and heavily processed food available. It is a high-carbohydrate (55%), moderate fat (30%) and low-protein (15%) diet compared to the standard KD (fat 75%, protein 20%, carbohydrate 5%) [44]. There are many differences between ketogenic and western diets, as represented in Table 1.

Table 1: *Differences between ketogenic and western diets.*

Ketogenic diet	Western diet
The KD is a high-fat and low-carbohydrate diet that aims to limit the dietary intake of glucose.	High-fat, high-carbohydrate diets directly correlate with obesity and metabolic syndrome.
Well-documented therapeutic functions: manage obesity, metabolic function, and heart disease	Eventually, leads to weight gain, high blood sugar levels, insulin resistance, heart disease, mental health struggles, and ultimately, metabolic syndrome.
A controlled diet that increases satiety and prevents overeating	It is easy to overeat, and often leaves individuals hungry and wanting to eat more.

Protein-sparing, modified fast

Protein-sparing modified fast (PSMF) is a very low-calorie, high-protein diet that encourages patients to consume 1.2 to 1.5g of protein per kilogram of body weight per day to maintain lean body mass while losing weight [45]. PSMF essentially combines a very low-carb KD with a very low-calorie diet. People who adhere to the PSMF enter ketosis, but the PSMF differs from other KDs in that protein, not fat, serves as the primary source of energy [46]. People who follow PSMF often lose weight rapidly and significantly, which may appeal to patients and medical professionals [47]. In contrast to the KD, which might be considered long-term, the PSMF is not intended for long-term maintenance.

Therapeutic indications for the application of the KD

Recent evidence suggests that KDs can play an important role not only in the management of seizures, but applications are now diverse and ever-increasing for the management of symptoms in neurological disorders, multiple sclerosis, Type II diabetes, obesity, cancer,

intestinal disorders, respiratory compromise, and chronic pain [48,49]. Therapies targeting nutritional ketosis without extensive diet modification can improve cognition and cerebral blood flow in patients with Alzheimer's disease and may have other benefits. Short-term KD trials to improve performance have shown mixed results [50].

The KD is also under investigation for managing diseases related to lipid metabolism (cardiovascular diseases and fatty liver), imbalance in the intestinal microbiota, nonalcoholic fatty liver disease, polycystic ovarian syndrome, amyotrophic lateral sclerosis, inflammatory bowel disease, and irritable bowel syndrome [51-53]. The KD is often prescribed before prescription pharmacotherapy for infantile spasms, myoclonic-astatic epilepsy, Dravet syndrome, and tuberous sclerosis complex [54].

Contraindications to the use of the KD

A patient could benefit from a KD but also suffer from comorbidities or conditions that contraindicate its use. The list of various contraindicated conditions is listed in Table 2 [55].

Table 2: *Contraindications associated with the use of the KD.*

Contraindications to KD
• Liver failure
• Kidney Disease
• Type 1 diabetes
• Concomitant use of SGLT-2 inhibitors
• Pregnancy
• Breastfeeding
• Cardiac arrhythmias
• Recent stroke or myocardial infarction
• Heart failure
• Respiratory failure
• Elective surgery or invasive procedures
• Increased serum uric acid and abnormal lipid profile

Molecular and cellular mechanism of action of the KD

The hallmark characteristics of the KD treatment are the production of ketone bodies, principally β-hydroxybutyrate, acetoacetate, and acetone, from the oxidation of fatty acids in the liver and reduced blood glucose levels. These KBs are produced in the liver and metabolized in extrahepatic tissues [56].

Ketone bodies act primarily as substrates for energy production, and a KD induces a pseudo-starvation metabolic state. Even within a single organ, each cell has its own metabolic bias depending on the cell type. Thus, assessment should be considered regarding the different molecular and cellular effects underlying various pharmacological effects of the KD (Table 3). In line with the growing evidence that ketone bodies are signaling molecules, several GPCR receptors, e.g., GPR41, GPR43, and GPR109A, have been shown to also bind to ketone bodies, thus playing an essential role in various aspects of ketone-body-mediated physiology [56].

Table 3: *Mechanisms of the functions of the KD exerting different physiological actions.*

Physiological role	Proposed underlying mechanisms of action	Reference
Epilepsy	Role of acidosis, dehydration, and increased ketone concentrations	[57]
Lipid metabolism	Without glucose, cellular energy is produced by degrading fatty acids. In addition, the KD induces the expression of fibroblast growth factor 1 and promotes the hepatic clearance of TGs.	[58,59]
Glucose metabolism	Initially, a KD promotes glycogenesis from amino acids and subsequently reduces the contribution of amino acids while the amount of glucose obtained from glycerol increases.	[60]
Gut microbiota	The KD alters the composition and diversity of the microbiota.	[61]
Type 2 diabetes	Reduction of plasma glucose, glycated hemoglobin levels, and serum insulin levels; improvement of insulin sensitivity	[62]
Obesity	Increased satiety, reduced lipogenesis, increased lipolysis, higher metabolic efficiency in consuming fats, and increased energy consumption	[62]
Nonalcoholic fatty liver disease	Low carbohydrates could decrease insulin levels with a consequent increase in fat oxidation and reduced lipogenesis.	[51,52]
Polycystic ovarian syndrome	Insulin resistance plays a role in the pathogenesis of PCOS. Fasting insulin shows a positive correlation with androgen levels in women with PCOS.	[52]
Alzheimer's disease	Neurons can use ketone bodies that may modulate the neuropathological and biochemical changes observed in AD. A KD can directly reduce the accumulation of amyloid plaques while reversing Aβ toxicity. Reduced oxidative stress, free radicle generation, and neuroinflammation.	[12]
Parkinson's disease	Reduced oxidative stress and the generation of free radicles. Exerted anti-inflammatory effects by decreasing the levels of pro-inflammatory cytokines.	[63]
Amyotrophic lateral sclerosis	A KD led to higher motor neuron survival, improved motor function, and increased mitochondrial ATP synthesis.	[64]
Depression and anxiety	The KD showed an antidepressant effect in animal models and human subjects. However, the underlying mechanism is unknown.	[62]
Cancer	Pro & con: could suppress sprecific tumors, but possibly worsen them in certain scenarios.	[62]
Heart Diseases	Ability to use ketone bodies as a source of energy by cardiac cells. A KD alters the pathway of energy metabolism and enhances the utilization of fat and ketone bodies through a very low-carbohydrate and high-fat diet.	[34]
IBD	The KD-modulated gut microbiota, contributing to alleviating colitis.	[65]
IBS	Reduces intestinal inflammation, improves cellular redox status, and restores mitochondrial function	[66]

Adverse effects and risks involved with the KD on the human body

The KD's short- and long-term adverse effects can be divided into mild, moderate, and severe or short-term versus long-term (Figure 1) [37]. Headache, constipation, diarrhea, sleeplessness, and backache are common and have mild side effects. Dyslipidemia, mineral shortages, metabolic acidosis, and an increased risk of kidney stones were among the moderate side effects. Furthermore, hypoproteinemia is often observed, which may be caused by the concomitant decrease in protein consumption [67].

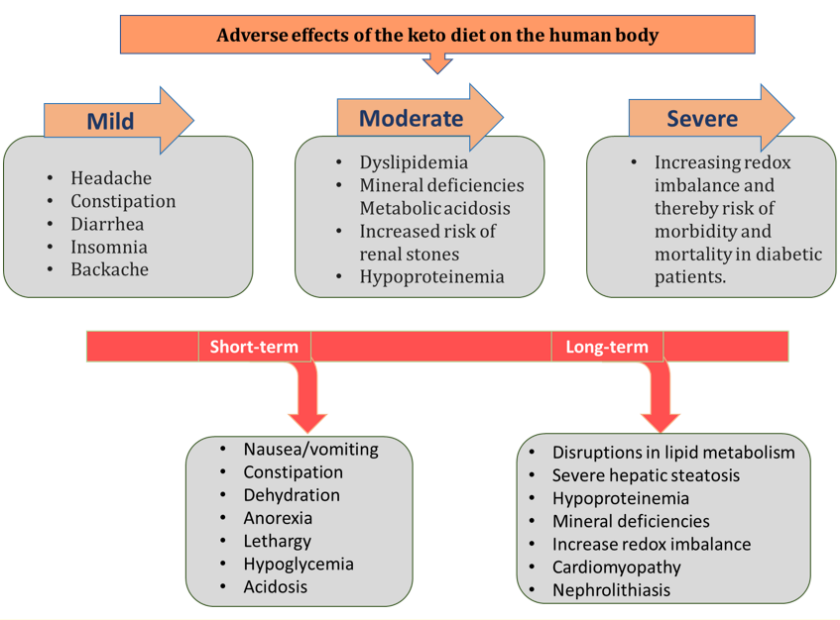

Figure 1: *Adverse effects of the KD. These are classified as mild, moderate, and severe based on the morbidity associated. It can also be short-term or long-term based on the duration of KD consumption.*

High amounts of ketones are associated with negative consequences, worsening redox imbalance and increasing the risk of morbidity and mortality in diabetes patients [68]. Dehydration, hypoglycemia, and moderate acidosis are some adverse outcomes that can be avoided or quickly addressed with mineral supplements, multivitamins, antacids, high-fiber vegetables, and sufficient fluids.

Other low-carbohydrate diets (LCDs)

Since 1860, and more recently in 1972, low-carbohydrate (low-carb) diets have been a strategy for weight loss. Today, there continues to be interest in low-carb approaches. Specific studies have defined low-carbohydrate as a percentage of daily macronutrient intake or total carbohydrate load. Low-carb diets are classified as follows:

- **A typical low-carb diet:** This diet does not have a fixed definition but is referred to as a low-carb or carb-restricted diet.
- **Low-carb, high-fat (LCHF):** It is a fairly standard, very low-carb diet, but with an even greater emphasis on whole, unprocessed foods. It focuses mainly on meat, fish and shellfish, eggs, healthy fats, vegetables, dairy products, nuts, and fruits.
- **Low-carb paleo diet:** The paleo diet involves eating unprocessed foods that were probably available to Paleolithic ancestors. Although not strictly low-carb, it can be modified to fit such a lifestyle. It emphasizes meat, fish, seafood, eggs, vegetables, fruits, tubers, nuts, and seeds.
- **The Atkins diet:** It is the best-known low-carb diet. It involves reducing all high-carb foods while eating as much protein and fat as desired. It is a 4-phase, low-carb eating pattern that allows a person to consume plenty of fat and protein. These 4 phases are termed. Phase 1: Induction. Eat less than 20 grams of carbs per day for 2 weeks; Phase 2: Balancing. Slowly add more nuts, low-carb

vegetables, and fruit; Phase 3: Fine-tuning. When one gets close to his weight goal, add more carbs until weight loss is slower; Phase 4: Maintenance. Eat as many healthy carbs as the body tolerates without gaining back the lost weight.

- **Eco-Atkins:** It is essentially a vegan version of the Atkins diet. It includes plant foods, protein, fat, gluten, soy, nuts, and plant oils.
- **Zero-carb:** This usually includes only animal foods, e.g., meat, fish, and eggs, and animal fats, e.g., butter and lard. Some of them also add salt and spices.
- **Mediterranean low-carb diet:** It is based on the traditional foods of Mediterranean countries from the late 20th century. A low-carb Mediterranean diet is similar to a regular low-carb diet. However, it includes more fish and extra virgin olive oil.

The advantages and disadvantages of the KD

Many people exaggerate the benefits of the KD, and it may look like an exciting train to jump on. Although the KD consistently shows its benefits in improving health-related issues, including chronic disease conditions, being satisfied with a limited variety of foods and not being allowed to have some more desired foods can be challenging to maintain. However, before starting a new diet plan, it is recommended a good idea to research and consider the pros and cons of the diet and speak with the a trained and knowledgable health care professional. Based on the adverse events reported in a number of published articles and physicians' opinions, the pros and cons regarding the KD are formulated in Table 4 [69].

Table 4: *Pros and cons of KDs.*

Pros	Cons
Weight loss In low-carb conditions, the body burns fat for energy- loss of body fat more quickly. Help eliminate cravings and feelings of hunger.	**Fewer carbs are not necessarily a good state** Some people (such as athletes) need to eat a high-carbohydrate diet, and a KD could result in less energy and endurance in athletes.
Helpful for desk-job individuals For people working "desk-job", the body does not need as many carbs and could function on a low-carb diet, like the KD.	**Chances of sugar deficiency** Sugar is an energy source for cells for proper organ functioning. For those who do not eat carbs, glucose could be inhibited from the bloodstream, making a person feel low energy and unable to focus.
It may prevent cancer Some studies have shown that there may be a link between very low-carb diets and cancer prevention. However, no clear evidence is reported.	**May induce a negative impact on heart health** Many foods that make up the KD are high in saturated fats and meat. These can increase cholesterol, often leading to heart disease risk.
Epilepsy The KD was first used clinically to treat and reduce seizures.	**Nutrient deficiencies** Because whole-food groups are excluded
Improved brain function Ketones help to strengthen and protect brain nerve cells and can improve feelings of anxiety and brain focus problems.	**Keto flu** Uncomfortable side effects due to diet transition

Criteria for recommending the KD

Children with epilepsy—who experience seizures despite taking antiepileptic medications—may benefit from a KD when implemented under the guidance of a physician or ddietitian [70].

Overall, an individual should consume less than 10% of total daily carbohydrates if one intends to follow a KD. Although more research on humans is required before this can be advised, there is growing interest in its use in cancer, particularly brain cancer [71].

Business outlook and marketing strategy of the KD

According to the report by Grand View Research (Report ID: GVR-4-68039-149-7): the global market size for the KD was valued at USD 9.57 billion in 2019 and is expected to expand at a compound annual growth rate of 5.5% from 2020 to 2027" [72]. The KD is marketed via supplements available in three major categories: powder, capsules, and oil, and it can satisfy nutrient requirements without many changes in a regular diet. As a result, the snacks segment is expected to expand.

Manufacturers are launching several snack products according to KD nutrients, which help people follow their diet and enjoy their meals. Major manufacturers promote their products through offline retail stores like hypermarkets and supermarkets.

Additionally, several companies are opening new brick-and-mortar stores worldwide to expand their customer base. As a result, KD manufacturers have a significant market share in North America, Europe, and Asia Pacific. Manufacturers are adopting several marketing strategies, i.e., new product launches, collaborations, and expansion of distribution channels.

Some prominent global KD market players include Ample Foods, Danone S.A., Nestle S.A., Keto And Company, Zenwise Health, Pruvit Ventures, Inc., Know Brainer Foods, Perfect Keto, and Bulletproof 360, Inc., among others [73].

Future perspective

Dietary interventions for treating and preventing diseases are now widely acknowledged and have gained increasing importance. Diet planning may serve as a medical approach for treating diseases and providing solutions to maintain health in the general population. However, the KD still faces challenges concerning broad clinical application [62]. Future high-quality randomized controlled trials are needed to provide high-quality clinical evidence on the efficacy and safety of the KD in diseases other than epilepsy. Contraindications must also be considered. Such studies might help modify the diet to increase tolerability and reduce adverse effects. A comprehensive understanding of the mechanisms of action of the KD might help in devising disease or patient-customized applications.

Estimates of biomarkers following the KD may guide the clinical use of the KD in various diseases. Deficiency in the long-tolerability of the KD introduces barriers to compliance by caregivers and patients. More modifications are required to boost efficacy and acceptability and should be created explicitly for certain diseases. Therefore, conducting more in-depth research on the intrinsic therapeutic mechanisms of the KD in treating various disorders is necessary. This process should offer new perspectives on disease pathophysiology and help pinpoint critical intermediary biochemical processes, chemicals, and other elements, including intestinal microorganisms, that control the effects of KD treatment. This process can then be used to build more specific and personalized interventional techniques that mimic the effects of a KD or as targets for drug creation.

Conclusion

The KD was designed initially as an epilepsy treatment in the 1920s and 1930s. Since then, the KD has shown potential applications in treating various conditions beyond epilepsy, such as obesity, neurodegenerative diseases, and malignancies.

For all of its potential benefits, the KD is challenging to maintain in the long term due to its strict dietary regime. Nevertheless, physicians—becoming increasingly aware of the KD's potential beneficial applications—recommend the KD in lifestyle modifications for specific conditions. With that said, some physicians remain uncertain of the KD's efficacy and safety.

The ketogenic diet is a high-fat, very low-carbohydrate diet, containing adequate protein intake and utilizing nutritional supplements, electrolytes, and hydration. This dietary combination creates ketones, similar to the fasting state. A controlled state of ketosis has distinct physiological and therapeutic advantages, e.g., altering multiple cellular signaling cascades, receptors, and biomarker levels in specific conditions. However, the ketogenic diet requires close monitoring as its dietary changes could adversely affect the dieting individual.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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