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Review

The Multifaceted Roles of Ketogenic Diets in Neurology-Brain Cancers and Other Neurologic Diseases

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Abstract

The ketogenic diet (KD) is currently well known in the lay media as a quick way to lose weight. However, the KD is not a new medical concept. The KD was used in the early 1900s to control seizures. However, as we developed more effective pharmacological agents, we used the KD less until it became practically obscure by the 1980s. Similar to the effects of fasting, the KD leads to the production of ketones as an alternative energy source to glucose. Therefore, the KD has many beneficial metabolic effects, such as an improved immune response, regulation of signal transduction, inflammatory pathways, and neurotransmission. There is growing evidence that KD can be used in the management of various disorders, such as mitochondrial diseases, metabolic disorders, and even cancer. From a neurological standpoint, the KD may have therapeutic benefits in multiple sclerosis, traumatic brain injury, dementia, and stroke. The purpose of this brief narrative review is to outline the current research in the literature

on the great potential of the KD as part of a comprehensive neurological treatment plan covering multiple neurological disorders such as status epilepticus, traumatic brain injuries, neurodegenerative diseases, autoimmune disorders, neuropathies, and cancers.

Keywords
Ketogenic diet; neurodegenerative disease; neurologic diseases; brain cancer; neurological treatment

1. Methods

We designed the search strategy of this narrative review to identify articles that investigated the relationship between ketogenic diet and neurodegenerative diseases, focusing on the mechanisms underlying the therapeutic effects of the diet. The search terms used were "ketogenic diet AND/OR physiology OR history OR neurodegenerative diseases OR oxidative stress OR mitochondrial dysfunction OR dementia OR seizure OR traumatic brain injury OR epilepsy OR cancer OR multiple sclerosis" and were applied to PubMed and Google Scholar, with the most recent publications up to 2022.

After the initial screening, we identified over 7525 articles collectively for all subtitles. and removed duplicates and irrelevant articles. Based on their relevance to the topic, we reviewed the full texts of the remaining 149 articles, and excluded 60 articles due to inadequate information, low quality, and for not meeting the inclusion criteria.

1.1 Inclusion Criteria

Articles related to the ketogenic diet, including its history, therapeutic uses, and effects on health; studies examining the effects of fasting and ketogenic diet on the body, particularly with regard to glucose homeostasis and metabolism; articles related to the role of oxidative stress, mitochondrial dysfunction, glucose, and ketone bodies in neurodegenerative disorders; and articles related to the mechanisms of action of the ketogenic diet in preventing seizures and treating epilepsy.

1.2 Exclusion Criteria

Articles not related to the ketogenic diet or ketones effects on health, articles that do not provide original research, such as editorials or opinion pieces, articles not written in English.

Overall, this review paper aims to provide an in-depth analysis of the current literature on the use of ketogenic diets in neurology, focusing specifically on their potential benefits for patients with cancers and other neurological diseases.

2. History of the Ketogenic Diet

In the early 20th century, fasting became increasingly popular because of its effects on minimizing seizure activity in patients with epilepsy [1]. Dr. Hugh W. Conklin and Bernarr Macfadden were two notable figures in the early 1900s, who hypothesized that fasting could help cure a variety

of human ailments [1-3]. Dr. Conklin assisted Macfadden in successfully using fasting to treat epilepsy. Their work quickly attracted the attention of Dr. H. Rawle Geyelin, an endocrinologist at New York Presbyterian Hospital, who reported their findings of improved cognitive function at national medical conferences [1]. As their results became more promising, more individuals became interested in this concept. Drs. Stanley Cobb and W.G. Lennox of Harvard Medical School discovered in the early 1920s that starvation caused metabolic changes that caused the body to start burning fat instead of carbohydrates, improving seizure control as early as two to three days [1]. The "Ketogenic Diet" (KD) was later developed by Dr. Wilder of the Mayo Clinic, as a diet that induces a metabolic state similar to that seen during fasting conditions, allowing people who are unable to fast, to reap its benefits. He proposed that ketonemia could be as effective and sustained for longer periods of time than fasting [1, 4]. For many years, KD has been used to treat epilepsy in children, but as new antiepileptic drugs were introduced, fewer children were placed on KD. As a result, fewer practitioners are trained to use this diet [1]. In 1994, the Charlie Foundation (USA) and Matthew's Friends (UK) were parent-created organizations that raised public awareness of the benefits of KD for neurological disorders [5].

3. Physiology of Starvation and Ketogenic Diet

Blood glucose drops during the first few days of starvation. Subsequently, glycogen stores in the liver and muscle (neurons do not store glycogen) are broken down and utilized in a process called glycogenolysis. After approximately 12 hours, glycogenolysis slows and gluconeogenesis, the process of producing new glucose, begins. Gluconeogenesis occurs through several pathways. Glycerol, amino acids (except lysine and leucine) from protein, and lactate from red blood cells can all be used in gluconeogenesis to produce glucose. During fasting or exercise, carbohydrate levels drop and protein is limited, causing adipose tissue to break down and release free fatty acids (FFA) and glycerol. Mitochondrial beta-oxidation breaks down FFA to provide energy to many cells. However, the blood-brain barrier prevents the brain from utilizing long-chain fatty acids. Glucose is the brain's primary energy source. FFA cannot undergo gluconeogenesis in the brain, but FFA can still provide energy by breaking down into acetyl-CoA and glycerol. Acetyl CoA is used to form ketones, which easily enter the brain, convert back to acetyl-CoA, and feed back into the Krebs cycle to produce more energy [6, 7]. The KD content shares the same mechanism of ketone production as in starvation, allowing the body to thrive by using it as an alternative source of energy [8, 9]. Despite an increase in fatty acid and ketone production the level of nutritional ketosis in the KD is relatively low, and not life-threatening, unlike diabetic ketoacidosis (DKA), which is an unbalanced state of high uncontrolled ketone production, as seen in type 1 diabetes cases [10].

4. The Effects of Ketogenic Diet on Physiology

Fasting and KD share many metabolic effects, which is why the KD is sometimes referred to as a "fasting-mimicking diet". Fasting/KD affects glucose levels and metabolic pathways such as fatty acid synthesis and breakdown, insulin signaling, regenerative and longevity pathways, and the control of reactive oxygen species damage [11, 12]. Furthermore, several studies have recently been published on the benefits of KD in various neurological disorders. The proposed mechanisms include metabolic regulation, improved neurotransmission, increased neuroprotection and anti-inflammatory properties, and a reduction in oxidative stress [9, 12, 13]. Intracellular signaling

pathways are also involved in the metabolism of glucose, proteins, and fatty acids. Fasting and the KD can improve insulin and glucose balance by increasing SIRT1, inhibiting AMPK and PI3K/AKT/mammalian target of rapamycin (mTOR) signaling, and restoring mitochondrial function [14-17].

4.1 Oxidative Stress

Many neurodegenerative diseases have mitochondrial dysfunction and damage owing to increased oxidative stress caused by reactive oxygen species (ROS) [18]. Examples of ROS include hydrogen peroxide and superoxide anions. Uncoupling proteins are mitochondrial transporters found in the inner membrane that allow protons to leak from the intermembranous gap into the mitochondrial matrix. Uncoupling proteins are becoming increasingly involved in the regulation of neuronal excitability and survival [19]. The uncoupling effect reduces the proton-motive force, dissociates or 'uncouples' electron transport from ATP generation, and indirectly reduces ROS formation [20]. Although it appears that increasing uncoupling protein levels would reduce cellular energy production, other studies show that continuous overexpression of uncoupling proteins in neural tissues boosted cellular ATP and ADP levels by inducing mitochondrial biogenesis [21]. The KD has similar effects in boosting mitochondrial uncoupling proteins activity to considerably decrease mitochondrial ROS production [20].

In addition, ROS increases neuronal hyperexcitability by reducing gamma-aminobutyric acid (GABA) release from synaptic terminals [22]. GABA is the primary inhibitory neurotransmitter in the brain and is responsible for reducing neuronal excitation [23]. In addition, it is highly sensitive to oxygen. Thus, mitochondrial ROS can reduce GABA signaling, and increase neuronal hyperexcitability and seizures. The KD can enhance antioxidant superoxide dismutase, which increases GABA, lowers hydrogen peroxide, and relaxes neuron excitability [24].

4.2 Aging and Ketogenic Diet

Advanced age is associated with cell damage and a decline in the density of mitochondria positive for succinate dehydrogenase (SDH) activity. The KD helps counteract age-related decline, not only through its antioxidant effects but also by increasing the density of SDH-positive mitochondria [25]. Modern diets are highly glycemic and produce advanced glycation end products (AGEs), which can damage neural cells and accelerate the aging process [26]. The low carbohydrate content of the KD can reduce glycemia, and protect neurons from AGE damage.

5. Adult Neurologic Conditions

5.1 Status Epilepticus

It has been reported in the literature that KD successfully achieved status epilepticus (SE) cessation [27]. This shows that the KD may play a potential role in the treatment of SE. Studies have demonstrated that KD can reduce seizure frequency in SE patients who are refractory to treatment, even to the point of becoming seizure-free [28]. KD helps SE cessation in a number of ways. It increases GABA production, activates inhibitory adenosine, and decreases glutamate excitatory neurotransmission, resulting in decreased neuronal excitability [13, 29]. Furthermore, as previously

indicated, decreased oxidative stress and improved mitochondrial function in KD may aid seizure management [29].

Recently, it was discovered that a decrease in neurosteroid levels in the cerebrospinal fluid is associated with SE [30], which is known to be modulated by KD [31]. KD is also known to alter mTOR signaling, reduce histone deacetylase activity (HDAC), and boost peroxisome proliferator-activated receptor gamma (PPAR-gamma) activity, which promotes seizure control by lowering inflammation. [32, 33].

5.2 Ischemic Stroke

Ischemic stroke causes brain damage due to excitotoxicity and apoptosis, which occur immediately after the onset of the disease. A study of rats fed a medium-chain triglyceride KD three days before an induced stroke found that KD protected against motor deficits. When compared to non-ketogenic diet-fed control rats, KD-fed mice were able to move faster, balance better, and maintain symmetric hand and foot movements [34, 35]. This is explained by the fact that KD reduces excitotoxicity, inhibits apoptosis, and reduces oxidative stress to provide neuroprotection [34].

5.3 Traumatic Brain Injury

Traumatic brain injury (TBI) often results in massive edema, inflammation, ischemia, and eventually neuronal cell death. A study of patients with TBI discovered that inhibition of ketogenesis and elevation of lactate levels were observed in the affected areas [36]. Nevertheless, ketone bodies synthesized by the KD may mitigate some of this damage through diminishing trauma-induced brain edema, decreasing cytochrome C release and cell apoptosis, lowering cytokine production and inflammasomes, and increasing cytotoxic T-cell numbers [37-39]. Additionally, ketones restored the cerebral metabolic rate, which was reduced in TBI, and reduced the regions of contusion injury in rats with TBI who were fed a KD. Indeed, mouse models demonstrated improved cognitive and behavioral function after being fed a KD for up to 30 days following traumatic closed-head brain injury [40]. This could be explained by the fact that mice with TBI and fed standard diets had lower SIRT1 levels than mice with TBI and fed a KD, whose SIRT1 levels were similar to those of mice without TBI, as SIRT1 is known to regulate several metabolic pathways in the body [40, 41]. Another mouse study on TBI revealed that ketone beta-hydroxybutyrate was able to improve sensorimotor and spatial memory deficits in adult mice [42].

5.4 Neurodegenerative Disease

Although the cause of age-associated senile dementia is not fully understood, beta-amyloid accumulation and neuronal and synaptic loss appear to be related to dementia in general [43]. A review of the literature reveals a number of potential risk factors for dementia, including mitochondrial dysfunction, age-related immune changes, chronic traumatic brain injury, uncontrolled hypertension, HIV infection, aluminum deficiency, poor nutrition, and the accumulation of AGEs [11, 44-54]

KD appears to be beneficial for neuroinflammatory and neurodegenerative diseases by activating PPAR to restore mitochondrial function and ATP production, and encouraging GABA release to

restore neurotransmitter balance, while also inhibiting insulin, PI3K/AKT/mTOR signaling, and increasing SIRT1 to delay aging and mitochondrial dysfunction [11, 14-17].

Moreover, KD may prevent dementia by protecting hippocampal neurons from amyloid-beta damage, improving glucose homeostasis and insulin sensitivity to restore mitochondrial function, and preventing the build-up of AGE products [11, 44, 53, 55].

5.5 Hereditary Neuropathies

Leber hereditary optic neuropathy (LHON) is an incurable, inherited maternal neuropathy that often affects young adult males. It frequently affects both eyes and results from mitochondrial defects. Specifically, a defect in the oxidative phosphorylation chain's complex I leads to an increase in ROS damage and, in turn, a reduction in the ATP energy that normally fuels cells. Calorie-restricted KD is being investigated as a promising therapeutic option to improve the ability of damaged mitochondria to produce ATP [56].

5.6 Multiple Sclerosis

Multiple Sclerosis (MS) is viewed as an immune-mediated disease that crosses the blood-brain barrier to cause demyelination and progressive motor debilitation. Inflammation is considered a likely cause of MS in most studies [57]. Treatment with a KD resulted in reduced proinflammatory enzymes such as cyclooxygenase (COX) 1 and 2, lipoxygenase, and arachidonate 5-lipoxygenase (ALOX5) in patients with MS compared to controls [58]. Furthermore, the gut microbiota may also play a role in autoimmune MS. The volume and diversity of gut and stool bacteria in MS patients are low and less diverse than those in individuals without MS. Ten MS patients underwent a KD for six months and had significant alterations in gut flora compared to control patients, but the bacteria reverted to baseline after the KD was discontinued [59]. Although MS is thought to be inflammatory in nature, few patients with MS do not have underlying inflammation [60]. In fact, there could be a neurodegenerative component driving MS, primarily driven by mitochondrial dysfunction, for which KD could be beneficial [61].

5.7 Amyotrophic Lateral Sclerosis

Currently, there is no cure for Amyotrophic Lateral Sclerosis (ALS), which is a fatal disease characterized by progressive neuronal death. Mitochondrial dysfunction is a probable cause of premature nerve cell death, in which the KD may play a role by stabilizing cell membranes, generating mitochondrial ATP for energy, increasing the number of motor neurons, and improving survival [62-64].

5.8 Cancer

The KD has been found to be effective against cancer in a variety of ways as a co-adjuvant therapy [9]. There is growing interest in the effects of KD on brain cancer [65-69], particularly glioblastoma multiforme (GBM), based on the hypothesis that tumor cells require more glucose and have a limited ability to utilize ketone bodies. As a result, the KD suppresses tumor growth by increasing ketone bodies and decreasing glucose [70]. The KD also controls tumors by decreasing insulin and

insulin growth factor-1 (IGF-1), ultimately decreasing glycolysis and limiting glucose availability for an anti-tumor effect [71-73].

In addition to targeting glucose metabolism, the KD can also fight cancer by providing energy to normal cells while starving cancer cells. This is based on the presumption that cancer cells have dysfunctional mitochondria, and by feeding with mostly ketone bodies, the tumors will further die from ketogenic-induced stress [74].

Furthermore, tumors can invade and produce their own blood supply, a process known as angiogenesis. Angiogenic factors, such as vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α), and hypoxia-inducible factors (HIF1), promote angiogenesis. In a mouse glioma study, KD was found to reduce invasiveness and alter proteins that grow in blood vessels [75].

KD can also delay cancer development by causing epigenetic changes [76]. Ketones exhibit anti-histone deacetylase (HDAC) activity. HDAC releases the tightly wrapped coils of DNA by removing acetyl groups from histones, allowing gene transcription. HDAC inhibition by KD is a promising therapy, because high HDAC expression has been associated with numerous malignancies [77, 78].

Radiation therapy uses ROS to induce stress and destroy cancer cells. However, radiation is less effective in locations where the tumor has pockets of hypoxia [79]. A KD is thus a good option, as it may add "metabolic stress" to the radiation-induced stress. This combined method could effectively target hypoxic cancer cells that would otherwise be radiation-resistant. One study found that the addition of KD to radiation therapy altered the chronic expression of critical genes involved in radiation-induced inflammation, such as COX-2 and the nuclear transcription factor NF-κB, both of which are implicated in radiation resistance [80]. This illustrates that the KD has clinical potential for the treatment of radiation resistance.

Stemness is also thought to increase the risk of cancer development. KD affects stem cell metabolism by increasing ROS levels and decreasing glioma cell proliferation [69]. HIF-1 alpha, mTOR, and B-cell lymphoma-2 (BCL2) expressions were also reduced, indicating that a KD had an anti-tumor effect on cancer stem cells [69].

5.9 Neuropathic Pain

Chemotherapy-induced neuropathic pain is commonly observed in cancer patients receiving chemotherapy medications such as taxanes, vinca alkaloids, and platinum-containing therapies [81]. The pain can last for years and has a detrimental effect on a person’s quality of life. Platinum-based chemotherapy frequently inhibits adenosine signaling, resulting in painful neuropathies [82]. Adenosine, on the other hand, is a neuroprotective nucleoside that can alleviate neuropathic pain [83, 84]. Furthermore, chemotherapy promotes adenosine kinase upregulation, which acts as a "sink" for adenosine, lowering its neuroprotective effects [85]. According to previous studies, KD appears to provide analgesic effects by increasing adenosine levels via ketone bodies [86, 87]. Thus, the KD may aid in the alleviation of neuropathic pain.

6. Summary and Future Directions

Many neurological disorders are chronic, progressive, and incurable with pharmacological therapy alone. The mechanisms underlying how the KD approach can assist in treating many neurological illnesses are becoming clearer. The KD appears to improve cerebral metabolism by

increasing inhibitory neurotransmitters to prevent seizures, reducing the effects of neuronal damage from stroke and traumatic brain injury, preventing amyloid-induced damage in dementia, enhancing mitochondrial function in ALS, decreasing the inflammatory process in MS, and slowing the progression of cancer through metabolic and epigenetic changes in tumor signaling and gene expression. Ketone bodies are neuroprotective in drug-induced neuropathies and may stimulate mitochondrial biogenesis in inherited neuropathies. Although the potential benefits of the KD have been discussed, it is not widely understood as a treatment; thus, its implementation remains a significant challenge. In medical consultations, the integration of informative resources, such as ketogenic management applications, alongside verbal communication, can improve patients' literacy and enhance medical encounters. Such applications are effective in promoting positive attitudes and raising awareness about the KD as a management tool [88, 89]. Although many advantages of the KD have been discussed, more substantial data and randomized clinical studies on the KD are still needed to validate its clinical use and fill knowledge gaps regarding its underlying mechanisms in the treatment of various illnesses. In addition, there is a need for campaigns to educate the general public regarding the benefits of the KD in disease management.

Author Contributions

Dr. Abdullah S. Binsaeedu, Dr. Mustafa Khalifa, and Dr. Jocelyn Tan-Shalaby all played important roles in the development and completion of the project. Dr. Abdullah S. Binsaeedu participated in writing and editing the manuscript, and managing the references. Dr. Mustafa Khalifa participated in conducting the literature review and writing the manuscript. Dr. Jocelyn Tan-Shalaby played a vital role in developing the project, as well as overall conducting and reviewing the study.

Competing Interests

The authors have declared that no competing interests exist.

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