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The Effects of the Ketogenic Diet on Disorders of Central Nervous System

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Abstract

The ketogenic diet (KD) that focuses on forcing body to switch from burning glucose to burning fat for fuel, has recently been a subject of livid investigation in terms of being a viable therapeutic option for various disorders, starting with obesity, through neurological and neurodevelopmental disorders, to mental disorders such as schizophrenia. Emerging evidence suggests that it may be useful in treating these conditions. This article explores the possible role of KD in the treatment of those condition.

Methods: Extensive research was conducted using PubMed and Google Scholar. References from selected articles were included in the analysis.

Keywords: diet; fasting, epilepsy, schizophrenia, autism

1. Introduction

The ketogenic diet is a dietary regimen characterised by the limitation of the intake of carbohydrates, with the intake of protein remaining on moderate level and the intake of fatty acids vastly increased (high-fat, adequate-protein, low-carbohydrate), thus being sometimes called the low-carb, high fat diet. The main purpose of the ketogenic diet is to put the organism in the state of ketosis, in which, as a result of the shortage of glucose, endogenous ketones are produced in order to provide energy for the brain. The maximum amount of consumed carbohydrates needed to achieve ketosis depends on factors like age, physical activity and lean muscle mass, with physically active adults being able to go above the level of 50 g of carbohydrates a day and still achieving a stable state of ketosis [1].

In 1911, the first modern use of starvation for the treatment of epilepsy was noted. Two physicians in Paris reported that seizures were less severe in period of starvation. While this was the origin for the ketogenic diet, it wasn't until 1921 that any physician tried to generate ketosis. Dr. Rollin Woodyatt noted that under conditions of starvation, acetone, and beta-hydroxybutyric acid appear. Woodyatt also uncovered that acetone and beta-hydroxybutyric acid were observed if patients ate a low carbohydrate diet. Around the same time, Dr. Russell

Wilder theorized that ketonemia could be produced for therapeutic benefit, but with a low carb diet rather than starvation. He developed the term "ketogenic diet." Since that time the ketogenic diet has become widespread in the treatment of childhood epilepsy. As better epilepsy medications were developed throughout the twentieth century, the ketogenic diet was used less and less frequently, although it has regained interest in the last 2–3 decades due to its capacity to treat seizures in pharmacoresistant patients. In the 1970s, nutritional ketosis was introduced as an idea for weight loss by Dr. Robert Atkins. In his book published in 1972, he describes how reducing carbohydrates "creates a unique chemical situation in the body…ketones are excreted, and hunger disappears." Many other low carb diets have also been popularized since the 1970s, from the South Beach Diet to variations of the Paleo and Mediterranean diets as a mainstream option for weight loss. As research has investigated the mechanisms behind ketosis and weight loss, the ketogenic diet has become in focus of several therapeutic approaches [2].

The ketogenic diet (KD) in conventional medicine is used mainly to treat hard-to-control (refractory) epilepsy in children, however, is also considered a mainstay therapeutic option for glucose transporter type 1 deficiency syndrome.

2. Ketogenesis

Ketones (ketone bodies) are water-soluble molecules containing ketone groups that liver produces when it breaks down fatty acids in a process called ketogenesis. These liver-derived ketone groups, being products of the processing of acetyl-CoA, include acetoacetic acid (acetoacetate), D-B-hydroxybutyrate (the precursor of acetone and acetoacetate that constitutes half or more of the total ketone bodies), and acetone, a spontaneous breakdown product of acetoacetate. Ketones are released into the blood after glycogen stores in the liver have been depleted (typically within the first 24 hours of fasting). In this way, ketones can be used by the body as an alternate source of energy.

Body uses ketones for energy during periods of caloric restriction of various scenarios: in the absence of carbohydrates, long periods of exercise or low food intake. Also, during untreated (or inadequately treated) diabetes, lack of insulin causes body to use fat for energy forcing liver to produce ketones. When ketones build-up in the blood, they can become acidic leading to diabectic ketoacidosis, which (esp. in type 1 diabetes) can be a life-threatening condition.

Ketone bodies are also produced in glial under periods of food restriction to sustain memory formation.

Thus, KD focuses on switching your body fuel source from burning glucose for fuel to burning fat for fuel.

However, ketones' properties go beyond an alternate source of energy.

3. The effect of ketones on metabolism

3.1. General effects

Ketogenesis takes place mostly in hepatocytes while ketone body utilization as metabolic substrates, or ketolysis, occurs mainly in the brain, heart, and skeletal muscles. Ketogenesis and ketolysis are regulated at the whole-body level by insulin (preventing ketogenesis) and glucagon (facilitating keto lysis) as well as fibroblast growth factor-21 promoting ketogenesis in the liver and ketolysis in peripheral tissues, including the brain. KBs and glucose metabolism are highly intertwined, and they present a reciprocal inhibition as a study in athletes undergoing nutritional ketosis shows a decrease in glycolysis and lactate production while increasing triacylglycerol oxidation in skeletal muscle. The switch of metabolic substrate preference occurred even with co-ingestion of carbohydrates and normal muscle glycogen, and despite physical workloads that would normally be highly glycolytic [3]. Ketones may influence both energy expenditure and energy intake. In general, ketosis does not have a major influence on energy expenditure but promotes a shift in substrate utilization towards ketone body oxidation. Ketone bodies stimulate modest insulin release, and they also feedback negatively on hormone sensitive lipase activity in adipocytes. Importantly, ketone bodies are preferred fuel in the brain during starvation [4].

3.1.1. Metabolic outcomes

The metabolism of ketone bodies interfaces with the tricarboxylic acid cycle, β-oxidation of fatty acids, de novo lipogenesis, sterol biosynthesis, glucose metabolism, the mitochondrial electron transport chain, hormonal signaling, intracellular signal transduction pathways, and the microbiome [5]. Ketogenesis is correlated with increased KB β-hydroxybutyrate and acetoacetate in blood and urine.

3. 2 Effects of ketone bodies on brain metabolism and function

Ketone bodies can cross the blood-brain barrier and be used as energy, especially when the levels of body ketones are high, they can provide energy to the brain and meet 60% of its

requirements [6]. In several investigations where ketone bodies have been used, it has been observed that they have a neuroprotective effect on nervous tissue [7].

The effects of ketone bodies on the brain have been widely investigated [8–10]. It has been noted that it has multiple ways of positively affecting the brain functioning, mainly via neuroprotection, neuroplasticity, epigenetics, nociception, changes in cell metabolism and anti-inflammatory properties. Studies show that it increases the number of neuroprotective factors, such as BDNF, GDNF, NT-3 and inhibits the activities of COX-2, thus resulting in halting the inflammatory response. It is worth noting that many neurodegenerative diseases or brain injuries are characterised by the disturbances of glucose metabolism in neurons, which, as a result, require another source of energy; in the case of brain trauma, for example, the brain's cells' amount of MCT channels (monocarboxylate transporters transporting ketone bodies) notes an 85% rise. The plausible conclusion is that there is a need of an energy switch, which is facilitated by high ketone production [6].

3.3 Effects on neurotransmitters

Glutamate is the major excitatory neurotransmitter in the brain. It must be continually synthesized and delivered to neurons the but also is rapidly and efficiently removed the synaptic space for two reasons: (a) maintaining low levels of glutamate in the synapse maximizes the signal-to-noise ratio upon release of this transmitter from nerve endings; and (b) a chronic elevation of glutamate in the synaptic space cause excitotoxicity and injure susceptible neurons, a factor present in many brain disorders [10].

One of the very first studies on brain metabolism and the effect of ketogenic diets suggested that shifting the source of ATP from glucose to KBs increased ATP:ADP ratios resulting in maintaining neuronal "stability" (i.e., resting state), thus reducing the frequency, duration, and/or intensity of depolarization events [11].

The proposed mechanisms for ketone bodies' (KBs) action on neuronal excitability involve glutamate and gamma-aminobutyric acid (GABA) signaling. In glutamate signaling β-hydroxybutyrate competes with chloride for the allosteric binding site of the vesicular glutamate transporter. The competition reduces the levels of glutamate inside the vesicles and reduces glutamatergic signaling.

Ketone bodies affect also GABA levels when β-hydroxybutyrate and acetoacetate are converted into Acetyl-CoA at a faster rate than with other substrates, which enters the Krebs cycle reducing the levels of oxaloacetate. To replenish the Krebs cycle, aspartate is converted to oxaloacetate, generating high levels of glutamate. Through the glutamate decarboxylase of

GABAergic neurons, glutamate is converted into GABA, increasing the intracellular GABA pool [12].

The potential mechanisms by which the ketogenic diet can exert an antiepileptic effect is via the influence on the aforementioned glutamate-glutamine cycle, which it presumably does in three different ways: a) via Increased Glutamine Synthetase Activity: Ketosis enhances flux through the astrocytic glutamine synthetase pathway, which helps "buffer" excess synaptic glutamate by promoting its uptake by glial cells; b) via enhanced GABA synthesis: More glutamine becomes available for GABA-ergic neurons, providing a larger pool of precursor for GABA synthesis, a key inhibitory neurotransmitter in the brain and c) via altered glutamate metabolism: Ketosis shifts the metabolism of glutamate, reducing its conversion to aspartate (via transamination) and increasing its availability for GABA synthesis through the glutamate decarboxylase reaction. Ketosis activates mitochondrial metabolism, particularly in glial cells, by increasing the use of ketone bodies (e.g., acetoacetate and 3-OH-butyrate) and acetate. This enhances the tricarboxylic acid cycle, leading to increased formation of glutamine and better regulation of glutamate levels. Additionally, ketosis may also affect how neurons handle glutamate, with increased glutamate available for GABA synthesis due to changes in metabolic pathways. The overall effect is an enhanced inhibitory neurotransmission, which could explain the antiepileptic properties of the ketogenic diet. What is worth noting is that even modest caloric restriction or a low-carbohydrate diet could improve seizure control, and that supplementation with compounds like acetylcarnitine, which may influence ketone body metabolism, could potentially be beneficial for epilepsy management [10,13].

4. Ketogenic diet in the management of brain disorders

Since ketogenic diets usually entail a myriad of systemic metabolic changes, their biological effects cannot be exclusively attributed to KBs. However, the significant rise in ketone bodies elicited by ketogenic diets prompted to hypothesize that KBs could have biological roles beyond metabolic fuel [14].

4.1 KD in epilepsy

Epilepsy is a group of chronic brain disorders characterized by recurrent epileptic seizures, affecting over 70 million people worldwide. Epilepsy is defined as: two unprovoked seizures occurring more than 24 h apart; a single unprovoked seizure if recurrence risk is high (ie, >60% over the next 10 years); or a diagnosis of an epilepsy syndrome. Epilepsy is

considered resolved for people who had an age dependent syndrome but have passed the applicable age and are seizure free, or in other cases of epilepsy, for those who have been seizure free for the past 10 years with no medication for the past 5 years [15].

Treatment-refractory epilepsy is a major problem in neurology. The pharmacological treatment available at the moment does not result in satisfactory seizure control in more than 30% of patients [16]. There are some other options, such as surgical treatment or vagus nerve stimulation, which yield somewhat positive results, yet only in small subsets of patients. Thus, the emergence of the ketogenic diet as a potential therapeutic option is so crucial to look into [16].

We do not know the mode of action of the ketogenic diet in controlling epilepsy. One possibility is that the diet alters brain handling of glutamate, the major excitatory neurotransmitter and a probable factor in evoking and perpetuating a convulsion. Brain metabolism of ketone bodies can furnish as much as 30% of glutamate and glutamine carbon also providing acetyl-CoA to the citrate synthetase reaction, in the process consuming oxaloacetate and thereby diminishing the transamination of glutamate to aspartate. Relatively more glutamate then is available to the glutamate decarboxylase reaction, which increases the brain level of gamma-aminobutyric acid (GABA). Ketosis also increases the level of GABA by increasing brain metabolism of acetate, which glia convert to glutamine. GABA-ergic neurons readily take up the latter amino acid and use it as a precursor to GABA. Ketosis also may be associated with altered amino acid transport at the blood–brain barrier. Specifically, ketosis may favor the release from brain of glutamine, which transporters at the blood–brain barrier exchange for blood leucine. Since brain glutamine is formed in astrocytes from glutamate, the overall effect will be to favor the release of glutamate from the nervous system [13] .

The KD is a therapeutic approach used in the treatment of epilepsy, especially in medication–resistant cases [17].

4.2 KD in depression

At a population level, sugar intake correlates with depression rates [18]. High glycaemic index diets appear to negatively affect mood. Furthermore, ‘comfort eating’ is common in mood disorders and carbohydrate cravings are often present in seasonal affective disorder [19] and atypical depression, which is common in bipolar dis order [20]. Reducing carbohydrate intake might therefore alleviate mood disorder symptoms in some individuals. Indeed, animal models of depression suggest that a ketogenic diet might exert an antidepressant or anxiolytic effect [21].

Case studies have also reported amelioration of psychotic symptoms following initiation of a ketogenic diet [22].

4.3 KD in autism

A KD may be an effective therapy for autism spectrum disorder by improvement its core symptoms but also benefiting its comorbidities, including seizures [23].

There are evidences that a KD improved the core features of autistic patients (Table 1) El-Rashidy et al. showed that a KD improved autistic manifestations, which was demonstrated as improved scores on the Autism Treatment Evaluation Test (ATEC) scales and the Childhood Autism Rating Scale (CARS), especially sociability improvement [24]. Evangeliou et al. also reported that a modified ketogenic diet applied for 6 months, with continuous administration for 4 weeks, interrupted by 2-week diet-free intervals improved the several parameters of autistic behavior and in accordance with the Childhood Autism Rating Scale suggesting that hat the ketogenic diet may be used as an additional or alternative therapy [25]. A case report of an ASD child found that a KD improved the electroencephalogram results and increased the child's intelligence quotient [26].

4.4 KD in schizophrenia spectrum disorders

Although there is no high-quality evidence of LC/KD efficacy in mood or anxiety disorders, several uncontrolled studies suggest possible beneficial effects [27].

It has been observed that KD reverses the sensory gating deficit in a mouse model of schizophrenia [28].

KD has shown some benefits in terms of mitigating the negative metabolic effects of second generation antipsychotics, as well as improving the general wellbeing, symptomatology and sleep quality in a 4-month pilot study [29].

In another study, the administration of KD in 31 treatment-refractory psychiatric patients resulted in substantial improvements in both psychotic and depressive symptoms [30].
In two case reports, 2 patients with treatment-refractory schizoaffective disorders experienced significant reduction in both negative and positive symptoms; the return of the symptoms after diet discontinuation was observed, with another amelioration after undertaking treatment again [31].

4.5 KD in Alzheimer's Disease

Impaired cerebral glucose metabolism may predict diagnosis and advance the pathogenesis of AD, the most common age-related dementia. It is well known that the brain has a very high energy requirement, mostly derived from glucose metabolism. As it is estimated that as much as 60% of the brain energy demand can be shifted to ketones, they are thought to have the potential to at least partially mitigate the brain energy failure seen in AD. Aside from being an alternative source of energy, ketones have also been shown in preclinical studies to protect against glutamate excitotoxicity, which is the principal mechanism targeted by the widely approved AD drug memantine [32].

Some preclinical and clinical studies have shown clear cognitive benefits associated with ketosis in AD (Table 1). Unlike other neurologic conditions, especially refractory epilepsy, where steady state ketosis is of critical importance, there is evidence to support a more intermittent approach in AD. However, clinical trials are thus far not addressing the impact of ketosis on AD pathophysiology. Several, but not all studies, show a clear impact of ketosis on both soluble and aggregated brain Aβ, and in some cases tau, yet no studies to date have examined this relationship in AD patients [33].

When ketosis is induced through a ketogenic diet, the production of ketone bodies increases, and βOHB reach plasma levels between 4 and 5 mM. In these ranges, it can have a neuroprotective effect, in some studies, it has been observed that it has such an effect on diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis [34,35].

Table 1. The use of ketogenic diet in the treatment of brain disorders

Author	Type of diet	Condition	Outcome
[17]	a classical 4:1 ketogenic diet after three months	Epilepsy	up to 85% of children achieved seizure reduction
[29]	macronutrient proportion 10 % carbohydrate, 30 % protein, and 60 % fat; at least 5040 kJ	Schizophrenia	participants with schizophrenia showed a 32 % reduction in Brief Psychiatric Rating Scale scores.
[29]	macronutrient proportion 10 % carbohydrate, 30 % protein, and 60 % fat; at least 5040 kJ	Bipolar	for both bipolar and schizophrenia populations, 43 % of participants achieved recovery
[36]	ketogenic diet	Bipolar	Case study, the KD led to full remission of the disease, reduction of lamotrigine doses and complete discontinuation of quetiapine.
[24]	ketogenic diet and modified Atkins diet, 6 months	Autism	improvement in ATEC and CARS scores.
[25]	ketogenic diet, 6 months	Autism	18/30 had an improvement in CARS.
[37]	Ketogenic diet, 32-week total study	Alzheimer's disease	Improvement in ADCS-ADL and QOL-AD. No change on ACE-III
[33]	Ketogenic diet, 12-week total study	Alzheimer's disease	No change is cognitive outcomes. Increased CSF Aβ; reduced CSF tau

ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; ACE-III, Addenbrooke's Cognitive Examination-III; ATEC, Autism Treatment Evaluation Checklist; CARS, Childhood Autism Rating Scale

5.Side effects

Common side effects of a ketogenic diet, including headache, fatigue, and constipation, were documented.

Carbohydrate depletion in KD can lead to flu-like symptoms called the “keto flu” - a set of symptoms such as dizziness, fatigue, irritability, nausea and constipation [38,39]. This results partly from dehydration and electrolyte imbalances, which can be tackled with proper hydration and eating foods rich in sodium, potassium and magnesium [40]. Constipation is another common side effect, which results from lack of fiber in the diet. What may also ensue is negative alteration of gut microbiota composition. It can be mitigated, though, with incorporating keto-friendly foods rich in fiber, such as cauliflower [41]. Ketogenic diet may also lead to nutritional deficiencies due to its restrictive character. It is recommended to supplement with potassium, magnesium, calcium and vitamins B, C and E [42]. The risk of kidney stones increases due to urine acidity increase and urine citrate levels decrease. KD should be avoided in people with chronic kidney disease [43]. There are also some studies linking ketogenic diet to negative impact on bone health [44–46]. Caution is required when it comes to patients with type 1 diabetes, as KD teamed with insulin treatment may cause hypoglycemia [47,48].

It is noteworthy that a vast majority of the aforementioned side effects diminished substantially, reaching minimal to negligible levels beyond the third week of the study [49,50] (**Table 2**).

Table 2. Common side effects of a ketogenic diet

Side effect	Description	Duration	Management tips
Keto Flu	A group of symptoms like headache, fatigue, nausea, cramping, irritability appearing during the first days of adaptation to ketosis	Usually 2-7 days	Drink plenty of water, replenish electrolytes
Constipation	Decreased fiber intake can lead to difficulty in bowel movements.	Ongoing, unless addressed	Increase water and fiber intake (low-carb vegetables, flaxseeds, chia seeds).
Bad breath	A fruity or acetone-like smell of the breath due to increased ketone production.	May persist as long as in ketosis	Maintain good oral hygiene, stay hydrated, chew sugar-free gum, and drink green tea.
Electrolyte imbalance	Reduced levels of sodium, potassium, and magnesium can cause muscle cramps, dizziness, and headaches.	Can occur early in the diet	Supplement with electrolytes and drink mineral-rich water (e.g., coconut water).
Increased cholesterol	Some people may experience a rise in LDL cholesterol and total cholesterol.	Can be long-term, monitor periodically	Focus on healthy fats (avocado, olive oil, nuts) and consider omega-3 supplementation.
Dehydration	Keto can have a diuretic effect, leading to fluid loss and dehydration.	Can happen early on	Drink more water, add electrolytes, and consume hydrating foods (like leafy greens).
Nutrient deficiencies	Lack of certain vitamins (e.g., vitamin D, calcium, magnesium) and minerals due to restrictive food choices.	Long-term, if not managed	Supplement with multivitamins and ensure a varied, balanced keto diet.

5. Conclusions

Ketogenic diet seems a promising tool in managing some difficult-to-treat and refractory disorders of the central nervous system. The reviewed studies show its potential as a co-treatment in ASD, schizophrenia spectrum disorders, bipolar disorder and Alzheimer's disease. Undoubtedly, there is a need for more robust clinical studies performed to better assess its efficacy in treating these conditions.

6. Limitations

However, there are limitations for some patients who want to use a ketogenic diet. Especially, patients who live with liver failure [51], pancreatitis [52], congenital disorders of fat metabolism , deficiency of carnitine palmitoyl transferase, carnitine translocase, porphyria, and pyruvate kinase will not be candidates for a ketogenic diet. Caution is also advised in terms of people taking certain medications, in particular for diabetes and blood pressure, which should be reduced. An additional limitation of the implementation of a ketogenic diet is that during the adaptation period, they could have side effects such as fatigue, headache, dizziness, nausea, vomiting, constipation, and low tolerance to exercise, even this symptomatology has been called the keto flu [53]. Another limitation is the character of the diet, which may be burdensome for patients to stick to, which could result in noncompliance and falling out of ketosis [54]

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