The Ketogenic Diet Revisited – evaluation of the ketogenic diet in neurological disorders

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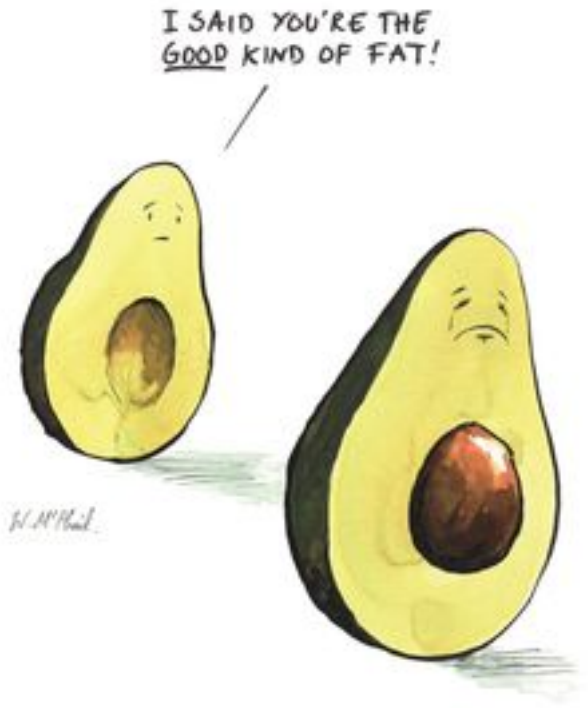
Bachelor Thesis



Abstract

The ketogenic diet (KD), which is a high fat, moderate protein and low carbohydrate diet, has been used for many years as a therapy for children with uncontrollable refractory epilepsy. Although its use has been shown to be anticonvulsant, its mechanism is still not clear. Due to the high fat content of the KD, it may evoke many side effects. Therefore it is highly recommended to initiate the diet under strict medical supervision. Although the diet is restrictive and challenging to follow, the symptoms of uncontrollable refractory epilepsy are decreased. In the course of the years, different potential applications of the diet are being investigated. Especially the use of the KD in neurodegenerative disorders including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis are thought to be effective. This is probably the effect of the mitochondrial dysfunction in neurodegenerative diseases wherein the ketogenic diet plays a pivotal role. The high fat content of the diet activates uncoupling proteins in mitochondria, which in turn decrease reactive oxygen species, which promotes mitochondrial fission and fusion processes. Although the diet seems to be a magic bullet for many still untreatable diseases, the timing of initiation of the KD must be considered. In addition, the quality of life of the patient after use of the KD should improve. By understanding the mechanisms of mitochondrial dysfunction in neurodegenerative diseases, the role of ketone bodies may be better understood. In the future, the ketogenic diet may not longer be seen as an alternative therapy, but instead as a standard therapy for untreatable neurodegenerative disorders. Taken together, it may be stated that the ketogenic diet is an underappreciated therapy.

Used Abbreviations

AcAc	Acetoacetate
AD	Alzheimer's disease
AGE	Advanced glycation endproducts
ALA	Alpha-linolenic acid
ALS	Amyotrophic lateral sclerosis
ATP	Adenosine triphosphate
BHB	β-hydroxybutyrate
Kcals	Kilocalories
KD	Ketogenic diet
LA	Linoleic acid
LGIT	Low glycaemic index treatment
MAD	Modified Atkins Diet
MUFAs	Mono unsaturated fatty acids
PD	Parkinson's disease
PUFAs	Poly unsaturated fatty acids
ROS	Reactive oxygen species
SFAs	Saturated fatty acids
UCPs	Uncoupling proteins

1. Under Appreciating the Ketogenic Diet

In 1994, a one-year-old boy named Charlie Abrahams suffered from many intractable and uncontrollable epileptic seizures [74]. Despite extensive medical interventions, including medications, hospitalizations and even brain surgery, Charlie's seizures continued unchecked, his development delayed and he had a prognosis of progressive retardation. Charlie's parents were in despair, but everything changed when they let him initiate the ketogenic diet (KD) at Johns Hopkins hospital in the United States of America. Miraculously, within several days after initiation of the diet, his seizures disappeared. Gradually taken off his medications, Charlie has remained seizure and medication free ever since [74]. This miraculous diet is composed of a high fat, moderate protein, and a very low carbohydrate diet [23]. Patients on the KD must consume 87-90% of their daily energy requirement as fat, which is twice of a typical Western diet [33, 66].

Although the ketogenic diet seems to be a successful therapy for uncontrollable epilepsy, the diet has fallen into obscurity due to the introduction of anticonvulsant medications in the late 1930s. In the 1920s, when current antiepileptic drugs were not available, the ketogenic diet was an effective treatment for children with difficult to control epileptic seizures. In a systematic review, 26 studies (which includes a total of 972 children with difficult to control seizures) were investigated on the efficacy of the ketogenic diet [32]. Six months after diet initiation, an average of 15.6% of the patients had become seizure-free, while 33% were reported to have more than 50% reduction in seizure frequency. Although these results were very promising, the mechanisms underlying seizure protection induced by the ketogenic diet were poorly understood. In the late 1930s, a new era of medical therapy for epilepsy had begun due to the introduction of anticonvulsant drugs. Consequently the ketogenic diet decreased in popularity and was largely forgotten. However, even today, with many new anticonvulsant medications, 30-40% of people diagnosed with epilepsy continue to have difficult to control seizures, due to the fact that the available treatments do not control their seizures [66, 3].

Even though the ketogenic diet is mainly used as an alternative treatment for people with medication resistant epilepsy, the diet may have many other potential effects, including neurodegenerative diseases such as Alzheimer's disease [30] and Parkinson's disease [26], but also for diabetes [2], obesity [10] and even cancer [46]. Due to the resurgence of interest in the ketogenic diet, the diet may not longer be seen as an alternative treatment, but instead as an standard therapy for untreatable disorders. Therefore it may be stated that the ketogenic diet is an underappreciated therapy.

This article explains the KD including its effect and its applications. Next, the advantages of the KD will be discussed in different conditions in which mitochondrial dysfunction may play an important role. In addition, the potential limitations and side effects of this diet-based therapy will be discussed.

2. The Ketogenic Diet

A typical American diet consists of 2200 kilocalories (kcals) a day and derives about 50% of calories from carbohydrates, 35% from fats and 15% from proteins [37, 18]. In comparison, the ketogenic diet derives about 5% of calories from carbohydrates, 80% from fats and 15% from proteins [18]. Figure 1 shows the comparison of the caloric composition of a standard American diet versus the KD.

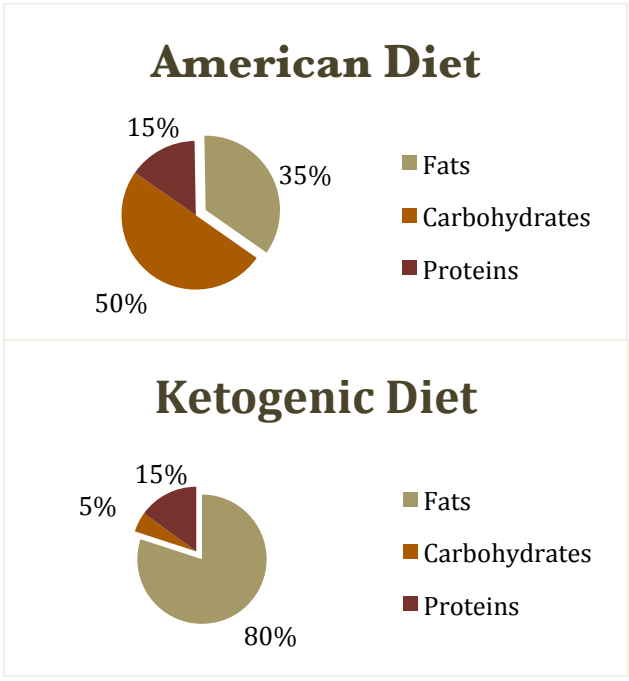


Figure 1: The caloric composition of the American diet vs. the ketogenic diet.

There are different types of fatty acids. Saturated fatty acids (SFAs) are the main type of fatty acids wherein adipose tissue is composed of, whereas the dominant fatty acids in muscle and other organ tissues are polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) [9]. The human body is capable of producing its own fatty acid needs from dietary intake, except for linoleic acid (LA), which is an omega-6 fatty acid, and alpha-linolenic acid (ALA), which is an omega-3 fatty acid. Therefore, omega-3 and omega-6 fatty acids are called essential fatty acids and in addition are PUFAs [9]. The type of fats that is consumed in the KD are SFAs. In order to improve the composition of fats, different types of oils are added to the diet, including sunflower oil and canola oil. In addition, foods rich in fats are added to the diet, such as nuts, cream and butter. The KD is insufficient in vitamins and dietary fibre, therefore supplements are added to the diet. Especially vitamin B6, vitamin D and calcium must be supplemented in order to maintain a healthy lifestyle [37]. Due to the high SFA content of the KD, patients show a high cholesterol blood level, which may be dangerous. The diet may be challenging and risky to initiate, therefore it is recommended to initiate the KD under medical supervision from a properly trained dietician. The specialist will evaluate the nutritional status of the patient where after a personalized meal plan could be set up [38].

The high fat content of the diet may evoke side effects. The most common complications include nausea, vomiting, constipation and diarrhea [18]. In addition, patients may show weight loss and mean cholesterol levels may increase, which is shown in a long-term ketogenic diet study of 24 weeks in obese patients [11]. However, the most common reason for discontinuing the diet is not due to the side effects, but lack of efficacy [18].

After initiation of the KD, the body will produce ketone bodies. The physiological role of ketone bodies will be explained in the next chapter.

3. Physiological role of Ketone Bodies

Under normal circumstances, carbohydrates are the main energy source in the human diet [28, 44]. The most important carbohydrate is glucose. In the presence of oxygen, most cellular energy is derived from metabolism of glucose by a process called glycolysis in mitochondria. However, under circumstances where glucose is limited, such as prolonged starvation or during the KD, the body undergoes metabolic changes to draw selectively on its extensive supply of energy from adipose tissue, sparing glucose for tissues that rely solely on glucose, i.e. red blood cells [47]. Thus, the utilization of carbohydrates and fats depends on glucose availability.

Due to the high fat and low carbohydrate content of the KD, an alteration in energy metabolism occurs, thereby forcing the body primarily to use fat as a fuel source instead of glucose. Fatty acids are oxidized in liver mitochondria into ketone bodies, which consist of three molecules: acetoacetate (AcAc), β-hydroxybutyrate (BHB) and acetone, [36]. Figure 2 shows the chemical composition of the three ketone bodies. Ketone bodies are the only alternative energy source to glucose. Due to the fact that the KD is composed of a high fat and low carbohydrate diet, it mimics the metabolic state of long-term fasting, thereby forcing the body into a metabolic state called ketosis. After the production of ketone bodies in liver mitochondria, the molecules are subsequently transported via the blood to extrahepatic tissues, where they are oxidized to generate energy by the production of the major energy transporter adenosine triphosphate (ATP).

Beta hydroxybutyrate is technically not a ketone body but a carboxylic acid due to its –OH group, which is formed from the reduction of AcAc.

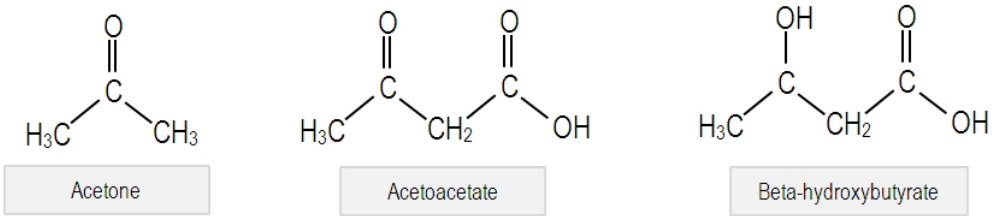


Figure 2: The chemical composition of the three ketone bodies: acetone, acetoacetate and β-hydroxybutyrate. [36]

Although the liver, kidney, heart and brain represent only about 5% of the total body mass, they have very high-energy requirements, contributing about 60% of the resting metabolic rate (which is the amount of energy used in a relaxed state) [44]. The brain cannot oxidize fatty acids [18]. Although fatty acids can cross the blood-brain barrier and the enzymes for fatty acid metabolism are expressed in the brain, it remains unclear why the brain cannot access the body's fat stores [47]. Therefore, it is highly important that ketone bodies are transported to the brain when glucose is limited. Compared to carbohydrates, which yield 4 kcal/gram, fatty acids are a very rich energy source for the body, with a yield of 9 kcal/gram [44]. Therefore it may be stated that utilization of fats are more effective than glucose. However, ketone bodies are still considered as an alternative energy source instead of a primary energy source. Due to the fact that the KD forces the body into ketosis, it may be stated that ketone bodies are the key role in the beneficial effect of the

Hibernating mammals use ketone bodies during hibernation in order to sustain metabolic activity under hypothermia and hypoglycaemia [19].

KD. By further understanding the role of ketone bodies during circumstances wherein glucose is present, the possible mechanism of ketone bodies during hypoglycaemia may be understood.

The KD and its production of ketone bodies are shown to be beneficial in children with refractory epilepsy. Due to the resurgence of the diet, more potential applications of the KD are investigated including for neurodegenerative diseases.

4. Potential applications of the Ketogenic Diet

The ketogenic diet has been used primarily in the treatment of refractory childhood epilepsy since the 1920s. However, due to the implementation of anticonvulsant medications in the late 1930s, its use declined dramatically. In addition, due to the fact that fewer children were placed on the KD, it resulted in a shortage of properly trained dieticians [67]. Luckily, the diet has experienced resurgence in use over the past 30 years. Since ketone bodies are an alternative energy source for glucose, the KD may have many other therapeutic uses in any disease in which cellular energy plays a role. There are clinical evidences that a diet may influence the human body [54]. Therefore, there are possible more potential applications of the KD.

Fasting has been used to treat epilepsy since at least the biblical times. There is a story about Jesus curing an epileptic boy. As Jesus says: "…this kind [demon] does not go out except by prayer and fasting" (Matthew 17:14-21).

The KD in seizure control

The reduction of blood glucose in the KD, which is a feature of caloric restriction, has shown to reduce seizure susceptibility [106]. The most common use of the KD is in uncontrollable refractory epilepsy in children [67]. Now, the KD is being used worldwide as an anticonvulsant therapy [34].

The KD in mitochondrial dysfunction

Due to the fact that ketone bodies are generated by fatty acid oxidation in namely liver mitochondria, the role of mitochondria in the KD are of importance. Mitochondria produce (particularly when dysfunctional) reactive oxygen species (ROS) and must be removed by the action of fission and fusion processes. Mitochondrial fission and fusion creates new organelles by the action of different proteins. Mitochondrial uncoupling proteins (UCPs) are activated by fatty acids and decrease ROS formation [100]. Mitochondrial dysfunction is a major cause of many neurodegenerative diseases. Since the ketone bodies appear to enhance mitochondrial function by decreasing ROS formation, the KD may play a pivotal role in neurodegenerative disorders, by possessing neuroprotective properties [1, 19]. In addition, the KD has been shown to stimulate mitochondrial biogenesis, resulting in stabilized synaptic function [57].

The KD in Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the leading cause of dementia [52]. It is associated with extracellular plaques containing the amyloid β protein in the brain. However, new results in experimental animal studies show that disruptions caused by an energy imbalance, may lead to AD [29]. Thus, the KD may have a beneficial role in patients with AD, and as suggested, clinical studies have been promising. In an in vitro study, cultured hippocampal cells were subjected to the ketone body BHB [66]. The investigators showed that BHB protects cultured hippocampal neurons against the toxicity directly induced by the addition of amyloid β. In addition, the KD may actually reduce levels of amyloid β deposition [63].

Another possible application of the KD in AD may be due Advanced glycation endproducts (AGE) [56]. AGE is a process of normal aging wherein proteins are glycosylated where after they may be dysfunctional. AGE accumulation is accelerated in AD, and due to the reduction of blood glucose in the KD, it may be seen as a therapy for patients with AD.

The KD in Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after AD [52]. The loss of dopaminergic neurons in the substantia nigra in the forebrain leads to tremor,

muscle stiffness and postural instability [52]. Tieu et al. showed that infusion of the ketone body BHB in mice injected with the neurotoxin MPTP (that cause dopaminergic neurodegeneration), protects from aging the dopaminergic neurodegeneration and motor deficits [62]. Additional evidence is provided by an in vitro experiment that pre-treatment with KD in mice alleviated the motor dysfunction induced by MPTP [68]. A therapy based on the KD might be beneficial for patients with PD.

The KD in Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that affects motor neurons in the brain and spinal cord. Death of motor neurons will lead to progressive weakness and loss of skeletal muscle and eventually in paralysis and death. A recent animal study suggests that ketosis induced by the KD might affect progression of ALS, by promoting ATP synthesis and bypassing inhibition of complex I in the mitochondrial respiratory chain thereby lowering the production of ROS [52]. Transgenic ALS mice that were subjected to a KD, showed a higher motor neuron survival and an improvement in motor function compared to knockout mice that were subjected to a standard diet. This result shows a neuroprotective effect by ketone bodies and a possible potential therapy for delaying ALS through a dietary intervention.

The KD in cancer

Cancer cells are highly dependent on glucose availability for growth, proliferation, energy production and transformation [66]. Since the KD decreases serum glucose, the diet may be added to the list of cancer therapies. As estimated, patients with newly diagnosed glioblastoma show a shorter survival rate when they have hyperglycaemia [15]. Glioblastoma cells cannot utilize ketone bodies as an alternative energy source [50], therefore the KD may be therapeutically beneficial for energy supply deprivation. In a pilot trial of the KD in 16 patients with metastatic tumors, five individuals reported improved emotional functioning and less insomnia, indicating that the KD may lead to improved quality of life [55]. The use of the KD as a cancer treatment should be further investigated in different tumor types in order to determine the potential of the KD for clinical use.

The KD in autism

Autism is a neurodevelopmental disorder that affects language and social development. In a clinical study, a modified KD diet was applied to 30 children with autism [16]. During this six-month pilot study, 60% of the children adhered to the diet and all showed major improvement. Although these data are preliminary, there is evidence that the KD may be used in autistic behaviour as an alternative therapy [41].

The KD showed its effectiveness in refractory epilepsy where after more other potential applications of the KD are investigated. Especially in mitochondrial dysfunction, ketone bodies might play a therapeutic role. Taken together, with the ability of ketone bodies to penetrate the blood-brain barrier, the KD may be a promising intervention for neurodegenerative diseases.

6. Future Perspectives

The ketogenic diet has been used for many years as a therapy for children with uncontrollable refractory epilepsy. Although its use has been shown to be anticonvulsant, its mechanism is still not clear. Despite lack of clinical data, there is emerging literature supporting the broad use of the KD. Although the KD is proven to induce ketosis [80], the KD is a challenging, restrictive and complicated diet. The diet requires strict compliance, precise meal preparation and food measurements, a lot of hospital observations and plenty of patience. For patients, the most common reason for discontinuing the diet is lack of efficacy. To make the diet more palatable and to provoke fewer side effects, alternative diets have been emerged, which is based on the same principle of the KD, which is a high fat- and a low carbohydrate diet. One of these alternative diets is the modified Atkins diet (MAD). Unlike the KD, the MAD involves no fasting, hospital stay, food weighing, or counting of calories. However, it still shows its efficacy in children with refractory epilepsy is similar to the KD [23]. In addition, the MAD is used in adults with refractory epilepsy, due to its palatable effect [33].

One potentially consideration of the KD is determining whether timing of initiation of the KD is of importance for a protective effect in all neurodegenerative diseases. Neurological disorders in late stages of progression may have extreme neuronal dysfunction, wherein the patient still must be able to palate the KD. In addition, if the patient shows extreme neuronal death, a KD may be late to recover its neuronal function. Besides, the quality of life of the patient after use of the KD should improve. Accera inc. investigates a solution, which is a company that makes Axona (AC-1202) [73]. The oral ketogenic compound was tested in subjects with probable Alzheimer's disease to examine if ketosis could improve cognitive performance. 152 subjects were daily administrated with Axona. AC-1202 rapidly elevated serum ketone bodies in AD patients [24]. In a 90-day clinical study, Axona enhanced memory and thoughts in some patients. The US FDA for the treatment of moderate Alzheimer's disease approved Axona (ACC-1202) as a medical food that is metabolized into ketone bodies. The company claims that Axona can increase the level of ketone bodies, even if glucose levels are normal or if carbohydrates are consumed [24]. Although its promising effect, many investigators raise their concerns about this compound, especially due to lack of information [49].

Another consideration of the KD is whether the long-term effects of the diet are profitable for the patient, compared to the side effects [11]. As mentioned before, the KD contains SFAs. However, the essential fatty acids omega-3 and omega-6 and many vitamins are not consumed. In addition, due to the high SFAs content of the diet, the majority of patients show high cholesterol levels after initiation of the KD [23]. An olive oil-based KD (which is high in MUFAs and low in SFAs and PUFAs) was studied in 121 children, however even rich in MUFAs-KD causes significant increase in cholesterol levels [22]. More studies are needed to determine the effect of KD on serum lipids using different fat sources in the diet.

A new era has just begun for the KD. Whether the KD will be a potential treatment or therapy for delay of symptoms is still the matter of debate. Due to lack of clinical data and an unclear view about the mechanism, the KD is still in clinical trial for a possible therapy. Nonetheless, the diet must not longer be seen as an alternative therapy, but instead as a probable new therapy for still untreatable disorders. Although the case of Charlie Abrahams may be a miracle, the ketogenic diet is still an underappreciated therapy.

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