The Ketogenic Diet: A Noteworthy Treatment For Pediatric Patients With Refractory Epilepsy

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ABSTRACT

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Although epilepsy has been a well-documented neurological disorder for thousands of years, a third of individuals with epilepsy today still have seizures that are not well managed. After the addition of benzodiazepines to other anticonvulsants in the 1950s, doctors have largely focused on treating epilepsy with medications. But, an older treatment has been recently reintroduced into the medical community to help remediate seizure activity. Interestingly, a high fat and low carbohydrate diet regimen called the ketogenic diet has proven to be helpful to some people with refractory epilepsy, that is, epilepsy that does not respond well to medications. In a number of cases, individuals with epilepsy who have failed over three attempts to control their seizures with medication become completely seizure-free after maintaining ketosis.

While the exact mechanism of the ketogenic diet treatment is unknown, many have their speculations. The diet is directly related to the diversity and quantity of gut microbiota, and is indirectly related to other biochemical structures and processes like mitochondrial efficacy and neurotransmission. The mechanism of action for the ketogenic diet in the treatment of epilepsy is likely a combination of interconnected biochemical mechanisms.

Although the ketogenic diet poses significant side effects for a small fraction of patients, the clinical benefits largely outweigh the drawbacks for most. The ketogenic diet and other

dietary variants are increasingly used in the remediation of epilepsy and other neurological

disorders.

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1.   Ancient Perspectives on Epilepsy

Since its first known documentation around 2000 B.C. in Assyrian texts, epilepsy has been a prominent disease described in a variety of languages and cultures. In ancient Babylonian texts, observers documented detailed accounts of what appeared to be seizures, and their apparent association with evil spirits. The Mesopotamians used the word *antasubbu*, relating to "the hand of sin and the God of the Moon," to describe a seizure (Jonathan Bird, 1991). Because seizures were believed to be caused by supernatural forces, individuals with epilepsy were treated spiritually or disregarded entirely in an effort to keep the evil spirits from affecting others (Edward H. Reynolds, 2005). Until the Hippocratic Collection of manuscripts was published in 400 B.C., epilepsy was exclusively documented as a magical phenomenon. In one of the manuscripts entitled *The Sacred Disease*, the author was the first to suggest a physical cause of epilepsy rather than a supernatural one. "It is not, in my opinion, any more divine or more sacred than any other diseases, but has a natural cause… Its origin, like that of other diseases, lies in heredity… the fact is that the cause of this affection… is the brain" ("On the Sacred Disease," translated by Francis Adams). The author argued that epilepsy was not actually a "sacred disease" and did not have a true connection to supernatural powers. To rid the body of seizures, he suggested, people should administer "whatever is most opposed… and not that which favors and is allied to it." At that time, healers and doctors used environmental elements such as wind direction, heat and cooling, and food as disease remedies. Because seizures are caused by a dysfunction in the human body, the treatment of seizures should be no different than

other diseases, suggested the author (Francis Adams, n.d.). Regardless of the opinions in the Hippocratic Collection, society continued to believe in the supernatural cause of epilepsy for centuries. Even in the New Testament that was written a few centuries later, epilepsy was still a feared disease; "when [someone] sees a madman or an epileptic, he gives a shudder, and spits into his own bosom" (Rev. John Kenrick, 1864).

2.   The 19th Century: The Classification of Epilepsy as a Neurological Disease

The first significant modern accounts that established a biological cause of epilepsy came in the 19th century. Robert Bentley Todd distinguished three different types of convulsions and described a phenomenon involving hemiparesis following a seizure, known today as Todd's paralysis. Further, he asserted a connection between epilepsy and the brain in his 1849 scientific publication entitled *On The Pathology and Treatment of Convulsive Diseases*. "We can localize the primary disturbance in the epileptic paroxysms… namely the hemispheric lobes and the mesocephale" (Robert Bentley Todd, 1849). John Hughlings Jackson, an English neurologist, described the migration and sequence of motor features in a focal seizure in 1868. Jackson suggested that these seizures did not come from just one cortical region, but instead traveled throughout the cortex, in areas that corresponded to the body parts affected during the seizure (*An Introduction to the Work of John Hughlings Jackson*, 2007). Through studying epilepsy in animals, neurologist Charles-Édouard Brown-Séquard proposed a hereditary component of epileptic convulsions. In the middle of the 19th century, French psychiatrist Jean Esquirol and his contemporaries, Calmeil and Georget, differentiated between somatosensory events, episodes of confusion or behavioral arrest, and motor events. Esquirol was among the first to suggest hospitalization in treating and managing epilepsy rather than imprisonment. Concurrent research on the electrophysiology of epilepsy by German physicians Eduard Hitzig and Gustav Fritsch also cast doubt on the supernatural hypothesis of epilepsy that dominated social thinking at that time. While the neurological basis of epilepsy prevailed into the 20th century in the medical

field, society was slow to accept this theory. Throughout the late 1800s, people with epilepsy

were still labeled as "criminally insane" and thus were commonly incarcerated (Owsei Temkin,

1945). Treatments rooted in neurology were still exceptions even at the turn of the century.

Physicians and healers still used herbal substances and environmental elements to treat epilepsy,

although most people with epilepsy were imprisoned and left untreated.

3.   The 20th Century: The Rise of Surgery and Pharmacological Treatments for Epilepsy

        Great advances in epilepsy treatment arose in the early 20th century. Before the 1900s,

surgical procedures were used sparingly in attempt to treat extreme cases of epilepsy. The risk

of infection, the logistical complexity of epilepsy surgery, and the challenge of locating specific

brain tissue to remove discouraged physicians from treating epilepsy with surgery. Trephination

was also documented as a successful treatment method, although it was likewise unpopular,

probably due to the incredible skill needed to complete the operation (William Feindel et al.,

2009). Simultaneous advances across Europe in the beginning of the 20th century helped

formalize one of the first neural procedures aimed specifically to remediate seizure activity: the

partial lobectomy. A German neurosurgeon, Fedor Krause, proposed that removing the cortical

area that causes seizure activity called the ictal zone would successfully terminate seizure

activity. Building upon this hypothesis, Krause's contemporaries focused on localizing

problematic brain tissue. Physicians and scientists across the world were racing to invent a

technology that would allow physicians to observe brain activity non-invasively. The first

electrophysiological monitoring device to do this successfully was the electroencephalogram

(EEG) invented in 1924 by German psychiatrist Hans Berger. By using the EEG, he quickly

became a pioneer in recording the electrophysiology of human brains. While Berger's 1929

publication detailing his EEG method and results was thorough, it was not widely accepted until

almost a decade later when others, including Adrian and Matthews, Fischer and Lowenbach, and

Gibbs and Davis, used the EEG to publish epileptiform discharges occurring during a seizure and

classification of a seizure in concert with the epileptiform activity (Benjamin G. Zifkin, 2009).

Around the same time in 1928, Wilder Penfield and William Cone created the Montreal

Procedure, a revolutionary surgical approach for epilepsy. In this approach, physicians used

local anesthesia to expose potentially epileptogenic cortical area while the patient remained

awake and alert in the surgical theater. Then, a small section of tissue was stimulated with

electric currents that either produced a seizure or a motor convulsion. If the induced seizure had

the same clinical features as a typical epileptic seizure for that patient, the stimulated tissue was

removed. The Montreal Procedure greatly improved the precision of epilepsy surgery and was

one of the first accounts of connecting seizure semiology with specific cortical areas (Lady

Diana Ladino et al., 2018).

At the same time, advances in anti-epileptogenic medications enabled people with

epilepsy to gain seizure freedom for the first time. Although potassium bromide was first used in

the 19th century to treat epilepsy, it wasn't until the early 1900s that the use of medications was

normalized. In 1912, phenobarbital was the first widely-synthesized pharmacological treatment

for epilepsy. A modified form of barbituric acid, phenobarbital aimed to decrease neural

excitation through sedation (Zifkin, 2009). This medication was the primary epilepsy treatment

for nearly two decades, until Tracy Putnam of the Boston City Hospital discovered phenytoin, an

anti-epileptic drug (AED) that was less sedative. Scientists in the 1950s began a significant push

to discover and release more AEDs, and as a result, carbamazepine, ethosuximide, and sodium

valproate, amongst others, were put on the market. For the following three decades, these AEDs

were the most popular treatments for epilepsy. Scientists introduced a second round of AEDs in

the 1990s and early 2000s including vigabatrin, lamotrigine, gabapentin, and topiramate.

4.   History of Dietary Treatments for Epilepsy

While surgical and pharmacological treatments for epilepsy were most distinguished throughout the latter half of the twentieth century, a third type of treatment option that arose in ancient medicine was reintroduced during the former half. For centuries, it was believed that the epilepsy could be cured only through dietary changes and herbal remedies. In 1911, French physicians Guelpa and Marie sought to study a common belief of the cause of epilepsy: fasting. Though their research documentation was brief, they discovered that seizures were less severe upon starving the participants (James Wheless, 2008). In the following decade, a few others reproduced Guelpa and Marie's results, and noted that seizure activity for most participants decreased around three days after the starving began. An American physician, Hugh Conklin, believed that epilepsy was caused by toxins in the body that damaged cortical areas in the brain. As a result, he attempted to cure epilepsy by starving his patients "as long as their physical condition allow[ed] it" (Emmanoiul Magiorkinis et al., 2014). For individuals with severe epilepsy that was untreatable with potassium bromide or phenobarbital, starving was a feasible treatment option in the first two decades of the twentieth century. However, physicians quickly noticed that fasting was not sustainable. Thus, they began to focus next on identifying the antiepileptogenic agents present during starvation such as neuroprotective biomarkers (ibid). In 1921, endocrinologist Rollin Woodyatt was studying diet in people with diabetes when he discovered that the levels of two ketones, acetone and beta-hydroxybutyric acid, were greatly elevated in people consuming a high fat and low carbohydrate diet and also in people who were

being starved (George Henderson, 2016). During that same year, Dr. Russell Wilder of the Mayo Clinic reported that the anticonvulsant effects of starvation could be reproduced using a diet that created ketones in the body. Named by Wilder for its ability to cause ketosis, the ketogenic diet became a possible treatment option for some people with epilepsy. It was Wilder's colleague, M.G. Peterman, who was the first to evaluate the effects of the ketogenic diet on epilepsy in a clinical experiment in 1924. In Peterman's study, seven of the twenty participants on the ketogenic diet became seizure free. Peterman also noted a number of unsuspected benefits of the diet, including "mental development… [that was] exceptionally good… decrease in irritability, and an increased interest and alertness" (Wheless, 2008). For the next decade, the ketogenic diet was used as a somewhat common epilepsy treatment in addition to the two medications phenobarbital and phenytoin. After the first push for an improvement in drug therapy in the 1950s, the ketogenic diet quickly became obsolete in treating people with epilepsy. With at least ten new anti-epileptic medications on the market, epilepsy for most was manageable only by taking a daily pill. Now, there were treatments that generated fewer side effects and were far less demanding than the ketogenic diet.

Despite the significant decline in dietary treatment research during this time, there were a few significant advances. In noticing that the restrictiveness of the ketogenic diet was the principal reason for the lack of patient interest in the diet, one physician wanted to explore other dietary regimens that still produced ketones but were more clinically practical. Dr. Peter Huttenlocher of the University of Chicago created a diet variant called the medium-chain triglyceride (MCT) diet in 1971 that did just this. While this discovery was significant, it

unfortunately did not result in a subsequent reestablishment of the ketogenic diet or its variants

as treatments for epilepsy. Then, in 1994 after NBC's *Dateline* aired an episode about the

ketogenic diet, dietary treatment was reintroduced into society. Since the airing of the *Dateline*

episode, the ketogenic diet has not only been used medically as a treatment for epilepsy, but also

socially as a weight loss regimen (James W. Wheless, 2008).

In recent years, the ketogenic diet has been used most frequently to help manage the third

of individuals with epilepsy that is not well controlled with medication.

5.   Clinical Definitions of Epilepsy

According to the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), a seizure is a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005). While seizures are most often imagined as the full-body clinical manifestation of abrupt body-jerking with perhaps foaming at the mouth, hand clenching, and eye deviation, they can take on many physical forms. Regardless of seizure type, all seizures have a clear beginning, middle, and end, and these distinct periods can often be determined clinically and by an electroencephalogram (EEG). Epilepsy is classified by the occurrence of at least one seizure and an elevated risk of seizure recurrence. This "enduring alteration in the brain" that suggests an increased probability of more seizures is critical in diagnosing epilepsy for individuals who have only experienced one seizure (ibid). According to the Epilepsy Foundation, a person can also be considered to have epilepsy if they have two seizures that occur more than twenty-four hours apart ("A Revised Definition of Epilepsy," 2014).

Seizures are classified under one of three different general categories based on their first clinical manifestation: focal onset, generalized onset, or unknown onset (Figure 1).

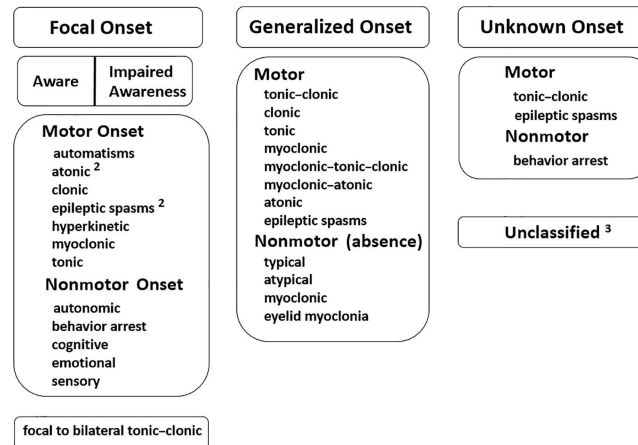ILAE 2017 Classification of Seizure Types Expanded Version [1]

Focal Onset

Aware | Impaired Awareness

Motor Onset
automatisms
atonic [2]
clonic
epileptic spasms [2]
hyperkinetic
myoclonic
tonic
Nonmotor Onset
autonomic
behavior arrest
cognitive
emotional
sensory

focal to bilateral tonic–clonic

Generalized Onset

Motor
tonic–clonic
clonic
tonic
myoclonic
myoclonic–tonic–clonic
myoclonic–atonic
atonic
epileptic spasms
Nonmotor (absence)
typical
atypical
myoclonic
eyelid myoclonia

Unknown Onset

Motor
tonic–clonic
epileptic spasms
Nonmotor
behavior arrest

Unclassified [3]

Figure 1: Expanded classification of seizure types from ILAE. Adapted from 'Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology' by R.S.Fisher et al, 2017, *Epilepsia*, p. 522-530.

Focal seizures can involve a stereotyped behavior, like one-sided arm jerking, and are manifested on the EEG as clearly initiated from one cortical region. They can be further classified into seizures with awareness, which pertains to individuals who retain any level of awareness during a seizure, or impaired awareness, which describes those who do not retain any awareness during a seizure.

Generalized seizures engage bilateral networks immediately, and, like focal seizures, can be classified as motor or nonmotor. Usually, clinical manifestations of a seizure can point clinicians towards classifying that seizure, and the EEG results can confirm this categorization (Fisher et al., 2017). Classifying a seizure can help diagnose an individual with a specific epilepsy disorder and determine an appropriate treatment plan.

Tonic-clonic seizures and epileptic spasms are classified in all three seizure categories, rendering them challenging to diagnose solely via clinical presentation. While the earliest clinical sign of a seizure may help classify that seizure, it may not be the most prominent part of the epileptic event. For example, a quick behavioral arrest can become a generalized tonic-clonic seizure with stereotyped, rhythmic limb jerking. Accordingly, this particular seizure may be classified as "focal onset with secondary generalization."

Epilepsy syndromes describe a group of features that include seizure type, etiology, family history, and EEG characteristics. Determining seizure etiology can be useful in both seizure classification and specific epilepsy syndrome diagnosis. Seizures of structural etiology are caused by abnormal neural structures that are distinguishable through brain imaging. These structural abnormalities can be caused by either genetic lesions or malformations, or acquired through traumatic events such as brain injury or stroke. Some patients with structural brain abnormalities may be candidates for epilepsy surgery, depending on the size, shape, and location of the lesion(s). As genetic testing is becoming more accessible and advanced, many epilepsies have recently been classified with genetic etiology. The mutation of specific genes, like PCDH19, SCN1A, and KCNQ2, cause seizures with predictable clinical features and age of onset, which allows clinicians to sometimes classify genetic epilepsies even before genetic testing. There are, however, a number of genetic mutations that likely cause epilepsy that have not yet been identified. Genetic epilepsy can also be inherited through complex inheritance patterns. According to ILAE, epilepsy of infectious etiology is the most common cause of seizures worldwide. This classification refers to an individual who develops epilepsy in the

setting of an infection such as HIV or cerebral malaria. Lastly, metabolic and immune seizure

etiologies describe seizures that are symptoms or complications of other disorders. Clinical

presentation, EEG characteristics, family history, and genetic testing allow clinicians to identify

the etiology of a given seizure (Ingrid E. Scheffer et al., 2017).

The diagnosis of an epilepsy syndrome can be helpful for many reasons, such as seizure

management, family planning, and patient prognosis. Epilepsy can begin at any time, including

the neonatal period, and can have an expected prognosis of seizures for just weeks to life

("Epilepsies: diagnosis and management," 2012). For example, benign familial neonatal

epilepsy is characterized by seizures around day 3 of life and are caused by mutations to two

genes that are related to potassium channels (S.F. Berkovic, 2004). Individuals with this type of

epilepsy only experience seizures for their first one to four months of life, and thus, do not

require an epilepsy management plan for childhood and beyond. A different epilepsy syndrome,

Dravet Syndrome, is usually caused by an SCN1A gene mutation and has an entirely different

prognosis than benign familial neonatal epilepsy. While it also begins in infancy, Dravet

Syndrome has a more intense symptom profile that will likely persist throughout the life of the

individual. Other symptoms and comorbidities of Dravet Syndrome include behavioral and

developmental delays, lack of muscle tone that leads to balance and mobility issues, delayed

speech, and sensory integration disorders. Due to this symptom profile, physicians often begin

aggressive treatment plans as early as possible as to minimize cognitive effects and other delays

related to Dravet Syndrome. These plans include the use of AEDs, especially clobazam, valproic

acid, Epidiolex, or the ketogenic diet ("Dravet Syndrome," n.d.). Determining the seizure

etiology for an individual with epilepsy can help define his or her seizure disorder, and

consequently assist in the implementation of an appropriate treatment plan.

6.   Initiation and Clinical Logistics of the Ketogenic Diet

The ketogenic diet is a high-fat, low-carbohydrate dietary plan used today both socially and to treat refractory epilepsy in pediatric patients. Historically, patients initiated the diet through a hospital admission and a subsequent 24 to 48 hour fast. Then, the diet was administered incrementally in the hospital through an increase in fat intake until the full 4:1 ratio was achieved (E. Lee et al., 2016). While this approach is most traditional, it may not be the most effective. There is some evidence that a gradual diet initiation is at least equally effective if not more effective than a fasting initiation (Suvasini Sharma and Puneet Jain, 2014). In the course of treatment, "fasting is no longer considered necessary to begin the diet" (Zupec-Kania 2008). Gradual initiation is the contemporary option for ketogenic diet initiation that increases dietary fat content throughout a few days before attaining the 4:1 diet ratio without initial fasting. Unlike the patients following a fasting initiation, those using a gradual initiation plan are able to eat one hundred percent of calories in each meal during this period. The gradual protocol yields fewer and less intense side effects like vomiting and hypoglycemia, and is more tolerable when compared with the fasting initiation protocol (A.C.G.Bergqvist, 2005). Some studies have reported a gradual calorie increase during the initiation phase with the 4:1 ratio beginning on Day 1. Regardless of diet initiation plan, the patient may remain in the hospital for one to two weeks for teaching and observation, but are typically discharged after three to five days (Eunjoo Lee, 2016). Ketonuria is observed in patients between 24 and 48 hours after diet initiation and must be attained before discharge. All medications that are used prior to dietary treatment

should remain the same throughout the dietary treatment period. During the diet initiation, the

patient and family meet with a dietitian to solidify a dietary plan specific to the patient. As the

ketogenic diet is most effective when the 4:1 ratio is attained, devising and adhering to a realistic

dietary plan is crucial. Patient and family compliance are necessary for treatment efficacy, and

the dietitian may be consulted as the patient is monitored during treatment. It is also necessary to

educate both the patient and the caregivers about nutrition and the possible side effects of the

diet, especially considering the young average age of treatment initiation. Throughout the course

of the diet, nutritional assessments and blood work are required to ensure healthy growth and

minimal side effects (Zupec-Kania, 2008).

The most prominent dietary treatment for epilepsy is the "classical ketogenic diet" also

known as the "4:1 diet." This feeding plan contains a ratio of four grams of fats to every one

gram of protein and carbohydrates. As it is challenging for some patients to ingest a large

amount of fat in their diets, patients who do not eat by mouth (via gastrostomy tube, etc.) find the

transition to the ketogenic diet easier (ibid). Some older patients report that the 4:1 diet is too

challenging and may be advised to try the 3:1 diet or another ketogenic diet variant such as the

modified Atkins diet (MAD) or low glycemic index treatment (LGIT). These diet variants

include less fat than the ketogenic diet and are reportedly easier to adhere (Figure 2).

		Macronutrient composition					
	Ratio	g/day			% of total kcal		
		Carbohydrate	Protein	Fat	Carbohydrate	Protein	Fat
KD	4:1	12	18	120	4.0	6.0	90.0
MAD	1.7:1	10.0	51.5	106.2	3.3	17.1	79.6
LGIT	0.66:1	30	90	80	10.0	30.0	60.0

Figure 2: Macronutrient composition for the ketogenic diet (KD), modified Atkins diet (MAD), and low glycemic index treatment (LGIT). Adapted from Lee E, Kang H, Kim HD. Ketogenic Diet for Children with Epilepsy: A Practical Meal Plan in a Hospital. Clinical nutrition research. 2016 Jan;5(1):60-3.

The ketogenic diet is rarely used for more than a few years. Patients typically see a decrease of seizure activity within a few weeks, however, the best results are achieved after a few months or longer. Because the diet involves significant dietary and lifestyle changes, patients seem more reluctant to continue this treatment if there are not remarkable benefits. Similar to their management of pharmacological treatments, physicians aim to eliminate the diet once the patient remains seizure free. Most often, individuals are on the ketogenic diet for three to twelve months (ibid).

The diet efficacy is assessed clinically through parent documentation in seizure journals. Blood work, including ketone levels, and frequent EEGs are used to monitor biochemical and neurological changes throughout the treatment period (Isabella D'Andrea Meira et al., 2019).

7.	Animal Studies in Dietary Treatment of Epilepsy

Animal studies allow clinicians to evaluate more dramatic fat:lipid ratio diet variants than the standard 4:1 diet. Furthermore, the use of animals is advantageous to evaluate methods of provoking seizures in both animal and human models.

Research conducted by scientists from Johns Hopkins School of Medicine in 2010 focused on determining the role of intermittent fasting compared with that of the ketogenic diet in anti-epileptogenesis. Mice were assigned to one of four groups: control, calorie-restriction by intermittent fasting, calorie-restriction by decreasing the amount of food intake per meal, and unlimited 6.5:1 fat:protein diet. Researchers implemented four different seizure tests on different individuals across all groups: the 6Hz test, intraperitoneal kainic acid, intravenous pentylenetetrazol and kainic acid, and maximal electroshock threshold. These tests induced seizures and helped evaluate the efficacy of each diet variant. For the 6 Hz test, the ketogenic diet group had improved protection from seizure activity, whereas the two calorie restriction groups experienced more easily-provoked seizures than the control group. Interestingly, the ketogenic diet had no effect on seizure activity in protection against the kainic acid tests, suggesting a distinction between the mechanisms of epileptogenesis in the 6 Hz and kainic acid tests. Where the 6 Hz test appeared to activate forebrain structures, kainic acid tests triggered activity in the hippocampus. Because the ketogenic diet was initially created to mimic the biochemical and subsequent clinical effects of fasting, it is intriguing that calorie restriction

through intermittent fasting and also through food deprivation at scheduled meals either did not improve or actively reduced the seizure threshold (Adam L. Hartman et al., 2010).

Kirk Nylen and colleagues from the University of Toronto conducted a similar study to compare the effects of the 4:1 and 6.3:1 diet in both adult and young rats. Using the pentylenetetrazol (PTZ) infusion test, they determined that the 6.3:1 diet elevated seizure thresholds in young rats but not in adult rats. This distinction between groups may have been related to the failure of the adult rats to reach the therapeutic range of beta-hydroxybutyrate levels. In addition, the neuroprotective effects of the 4:1 diet did not statistically differ from that of the control group for both young and adult rats. Because the young rats reached the therapeutic range of beta-hydroxybutyrate levels in this condition and did not experience an increase in seizure threshold, their ketone levels cannot completely account for the lack of seizure protection. In addition, Nylen mentions that the PTZ test "does not model human intractable epilepsy," but rather it simply allows researchers to compare the seizure threshold of subjects in each group. Presumably, this limits the external validity of this experiment, as comparing the effects of the ketogenic diet on this rat sample may or may not relate to actual seizure activity in human subjects (Kirk Nylen, 2005).

8.   Human Experiments in Dietary Treatment of Epilepsy

In the last decade, numerous studies have been performed to evaluate the clinical effects of the ketogenic diet. Specifically, researchers aimed to evaluate the efficacy of the traditional 4:1 diet in humans and compare the outcomes of the 4:1 diet with that of other diet variants, such as the 3:1 diet and the modified Atkins diet, in pediatric populations.

In 2008, Elizabeth G. Neal and her colleagues from the Great Ormond Street Hospital in the UK studied the use of the 4:1 ketogenic diet in 103 children who had greater than seven seizures per week and who failed at least two antiepileptic drugs. The two experimental groups in this study received either the ketogenic diet immediately or received the same diet after a 3-month delay with no change in AED treatment during the delay period. After three months, the diet group had an overall 38% reduction in seizure frequency of at least 50%, whereas the control group that did not receive treatment demonstrated a 37% average increase in seizure frequency. The most common side effects recorded were vomiting, constipation, lack of energy, and hunger (Elizabeth G Neal et al., 2008).

Researchers from Yonsei University College of Medicine conducted a similar study in 2007 involving seventy-six patients with refractory epilepsy to compare the 4:1 diet to the 3:1 diet. The diet ratios describe the lipid:non-lipid content of each diet. After sustaining the diet for three months, both groups reported overall favorable outcomes. 55% of the 4:1 diet group and 30.5% of the 3:1 diet group, respectively, achieved complete seizure freedom. After six months, there was no difference between groups in the maintenance rate of the respective diet

programs. While the maintenance rates were the same, individuals in the 3:1 diet group tolerated the diet significantly better than the 4:1 diet group, with only 13.9% reported gastrointestinal intolerance of the 3:1 group compared with 35.5% of the 4:1 group. Interestingly, blood ketone levels and other laboratory findings were not significantly different between groups at the three-month mark. In the second phase of the study, half of the seizure-free individuals on the 4:1 diet were switched to the 3:1 diet, and half of the individuals who failed the 3:1 diet were initiated on the 4:1 diet. After three months of remaining on a new diet variant, all of the patients in the original 4:1 group remained seizure-free when switched to the 3:1 variant. Conversely, although 75% of patients who switched to the 4:1 diet after unsuccessfully completing 3 months on the 3:1 diet had a 50% or greater decrease in seizure frequency, none became seizure free. Ultimately, the authors recommended the 4:1 diet for better efficacy and the 3:1 diet only for individuals with GI problems who would not easily tolerate the traditional diet (Joo Hee Seo et al., 2007).

K.N. Vykunta Raju and colleagues from a tertiary care hospital in India compared the effects of the 4:1 diet with an even less restrictive variant, the 2.5:1 diet, in the pediatric population of individuals with refractory epilepsy in 2011. For both groups, the diet was initiated at the hospital using a non-fasting, gradual initiation protocol. Both groups began on a 1:1 program and worked up to the final diet ratio by the end of the fourth day. The median seizure frequency for all participants was 11 seizures per day. At three months, the only significant differences in the lipid profile were an increase in low density lipoprotein for both groups and an increase in high density lipoprotein for only the 2.5:1 group. Interestingly, there

was no significant difference of seizure frequency between groups, with about 60% of both groups having a seizure reduction of at least 50% by three months. Constipation was reported as the most common side effect. The authors also introduced the idea of cultural food differences in the context of choosing an appropriate diet plan for individuals who wish to initiate the ketogenic diet as a treatment for epilepsy. As this study was conducted with Indian children, who traditionally eat consisting of two-thirds carbohydrates, the 2.5:1 diet may be the most realistic plan for these children and will allow for a higher adherence to treatment (K.N. Vykunta Raju et al., 2011). This variant may also be helpful for patients who have autism spectrum disorder (ASD) and typically eat a carbohydrate-rich diet.

A 1989 study demonstrated the clinical differences between the 4:1 diet, MCT diet, and modified MCT diet in fifty-nine pediatric patients. The modified MCT diet combined long-chain and medium-chain fatty acids into the diet. Although the number of participants in each experimental group was small (12 to 27), all diet variants were effective for patients. Overall, 81% of participants had a decrease in seizure frequency by 50% or greater, and the results did not statistically differ between diets. Children under fifteen years old achieved the greatest seizure reductions. Fourteen of sixty-two patients had improved EEGs at three months, whereas, interestingly, five EEGs deteriorated. This decline did not correspond to a subsequent clinical deterioration (Ruby H. Schwartz et al., 1989).

Within the specific population of individuals diagnosed with infantile spasms, Amanda M. Hong and colleagues from the Johns Hopkins Hospital evaluated the clinical outcomes of the ketogenic diet. A modified 3:1 or 3.5:1 diet was administered rather than the 4:1 diet to account

for the young age of the patients, as these individuals needed more protein for growth and development. The patients' parents reported an average of 1749 spasms per month before ketogenic diet initiation. At the three month mark, 73% of patients had a greater than 50% reduction in seizure frequency, with 18% completely spasm-free. Twenty-four months after patients began the ketogenic diet, 80% had a greater than 50% reduction in seizure frequency, with an astounding 33% completely spasm-free (Amanda M. Hong et al., 2010).

9.   The Effects of the Ketogenic Diet on Gut Microbiota

The gut-brain axis has been increasingly evaluated in the pathology and treatment of neurological diseases. As the ketogenic diet is a dietary treatment for epilepsy, the connection between the gastroenteric pathway and the central nervous system may be critical in understanding epilepsy. In the last decade, considerable research has been aimed at determining the effect of the diet on not only typical biomarkers in blood tests such as ketone levels, but also on gut microbiota. These microorganisms are one clear point of connection in the gut-brain axis that can not only alter biochemical processes in the body directly such as digestion, but also adjust a number of pathways indirectly (Xiqun Zhu et al., 2017). Gut microbiota promote immune system and mitochondrial function, alter neurotransmission, ketone metabolism, and even mood and cognition (Zhu et al., 2017, Christine A. Olson et al., 2018). Because the gut-brain axis is so extensive and interconnected, the alteration of any link between these two body systems can cause a variety of symptoms (Zhu, 2017).

For example, a case study from 2017 described an infant with refractory epilepsy of an unknown cause. When the infant stopped eating after contracting a viral infection, his also seizures stopped completely. Upon evaluation and diagnostic workup of this event, physicians discovered that his allergic reaction to cow's milk resulted in seizure activity. Eventually, the infant became seizure-free without AEDs while consuming cow's milk and protein-free diet (Raffaele Falsaperla et al., 2017).

Gut microbiota are also related to disorders like schizophrenia, multiple sclerosis (MS), and Alzheimer's disease (AD). Thus, they can be connected to normal and pathological neural

functions and structural characteristics ranging from memory to neuroplasticity to hallucinations. Studying the gut microbiota in neurological diseases and discovering additional quantifiable connections between the CNS and the gastrointestinal tract is pertinent to maximizing treatment efficacy for individuals with epilepsy (Zhu, 2017).

A 2017 experimental study from the Shenzhen Children's Hospital evaluated and compared the diversity and number of gut microbiota in healthy infants and infants with refractory epilepsy. Researchers concluded that the gut microbiota of health and epileptic group before ketogenic diet treatment significantly differed. Overall, the stool of epileptic patients contained enriched pathogens and reduced beneficial bacteria when compared with that of healthy patients. Interestingly, there were several changes to the gut microbiota of the epileptic group after ketogenic diet treatment (Figure 3). Specifically, *Bacteroides* and *Prevotella* increased after treatment, wherea*s Cronobacter, Erysipelatoclostridium, Streptococcus, Alistipes, Ruminiclostridium, Barnesiella, and Enterococcus,* all decreased after treatment (Gan Xie et al., 2017). A second study also noted the elevation in *Bacteroides* levels post treatment, and found that *Firmicutes* and *Actinobacteria* decreased. After the ketogenic diet, the gut microbiota diversity of individuals with epilepsy lessened overall (Egidio Spinelli and Robyn Blackford, 2018).
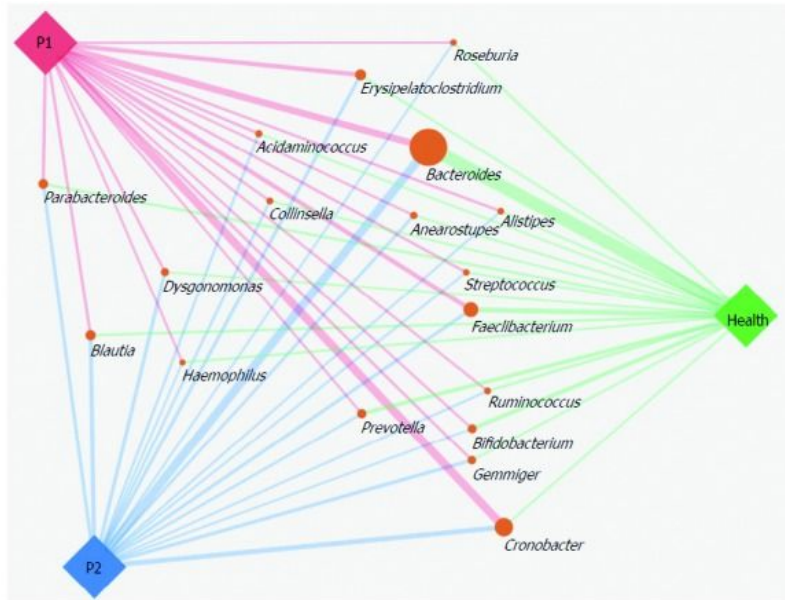
Figure 3: Gut microbiota in P1, P2, and Health groups. P1 is the group with epilepsy before ketogenic diet treatment and P2 is the same group after ketogenic diet treatment. Adapted from Xie G, Zhou Q, Qiu CZ, Dai WK, Wang HP, Li YH, et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. World J Gastroenterol. 2017 September 07;23(33):6164-71.

Researchers from the Department of Integrative Biology and Physiology at UCLA conducted an experiment to examine the neuroprotection of the ketogenic diet in mice and the gut microbiota changes that resulted from the diet. Feeding the mice a 6:1 diet, they used the 6 Hz test to measure seizure thresholds of the mice. A number of microbiota appeared in significantly different quantities between the control and ketogenic diet groups, as did the seizure thresholds after four days. When the microbiota produced in individuals on the ketogenic diet were transplanted into individuals on the control diet, the mice developed significantly better seizure control than the control diet group. Also, the mice that were transplanted with the control diet microbiota but were consuming the ketogenic diet still demonstrated significantly greater

seizure protection than that of the control group. Because the 6Hz test does not have high

construct validity for human epilepsy, Spinelli and Blackford also modulated gut microbiota in

Kcna1$^{-/-}$ mice. By mutating one of the subunits in a gene for the voltage-gated potassium

channel, this mouse model more accurately mimics temporal lobe epilepsy in humans. The

groups of Kcna1$^{-/-}$ mice were treated with either a control solution or *A. muciniphila* and

Parabacteroides, two bacteria that are significantly increased during the ketogenic diet

treatment. Then, the mice were fed either a control diet or ketogenic diet. Administering the

bacterial treatment before the diet significantly decreased both the number and duration of

seizures per day of the mice on both diets, even when compared with mice treated with
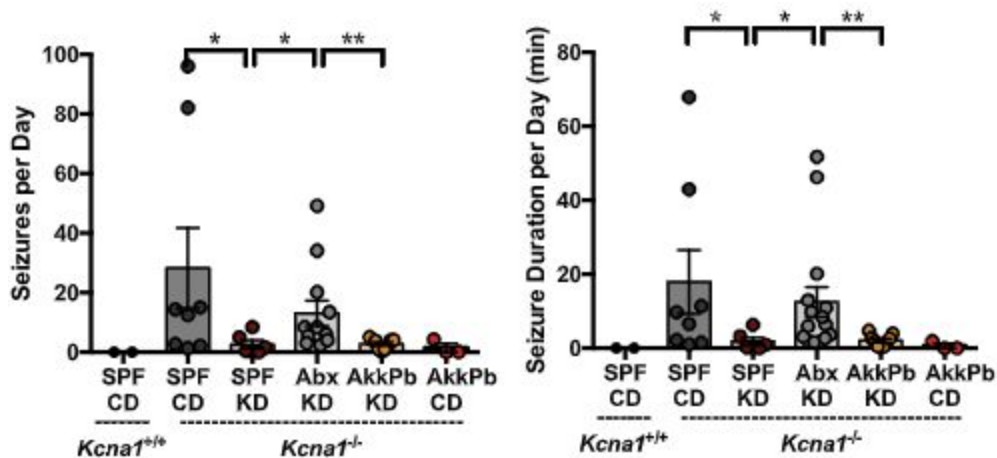
antibiotics on the ketogenic diet (Figure 4).

Figure 4: The average number of seizures per day and average seizure duration per day of Kcna1$^{-/-}$ mice conventionally colonized specific pathogen free (SPF), treated with antibiotics (Abx), or treated with *A. muciniphila* and *Parabacteroides*. The mice were fed either a control diet (CD) or the ketogenic diet (KD). Adapted from Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY. The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet. Cell. 2018 June.

This suggests that gut microbiota are both "necessary and sufficient" in decreasing seizure frequency and duration for temporal lobe epilepsy in mice (Christine A. Olson et al., 2018).

The gut microbiota that are altered through dietary changes such as the ketogenic diet directly affect seizure activity in both humans and animal models. While quantifying and evaluating the gut microbiota is increasingly pertinent to understanding epilepsy, there may be additional points along the gut-brain axis that provide a more complete picture of the pathology of epilepsy.

10.   Biochemical Mechanisms

The biochemical mechanism of anti-epileptogenesis of the ketogenic diet is widely discussed, as there are endless points of connection between the gastrointestinal pathway and the central nervous system. It is likely that the ketogenic diet mediates a number of pathways that together create an anticonvulsant effect.

According to a recent study from the Legacy Research Institute in Portland, OR, beta-hydroxybutyrate "has been considered as the main effector of the therapeutic benefits of ketogenic diet therapy" until 2017 (Detlev Boison, 2017). Direct anti-seizure effects of two ketone bodies were first observed in animal experiments in the 1930s; since, all three ketone bodies have demonstrated neuroprotective effects (Suvasini Sharma and Puneet Jain, 2014). The shunting of ketones in the brain to oxidative metabolism increases the number of amino acids created through metabolism, especially GABA. Although ketone bodies increase inhibitory neurotransmission and/or decrease excitatory neurotransmission in the brain, GABA and glutamate levels do not significantly differ between individuals with and without epilepsy (Boison, 2017). While some studies have supported the increased neural inhibition hypothesis, others, including some animal studies, refute it (Jong M. Rho, 2017).

A second possible mechanism of action involving inflammatory pathways and peroxisome proliferator activated receptors (PPARs) has also been identified in the antiepileptogenic effects of the ketogenic diet in epilepsy (Boison, 2017). In epileptogenesis, the production of reactive oxygen species is modified. Because PPARs function as anti-inflammatory and antioxidant mediators in the human body, their mutation may correspond

to seizure activity. PPARγ, a subunit of the receptor, is activated by fatty acids. As the ketogenic diet greatly increases the bioavailability of fatty acids such as arachidonic and decanoic acid, PPARs are activated more often during treatment. Timothy Simeone and colleagues from the Creighton University School of Medicine in Omaha, NE discovered that in mice, the diet selectively increased the activity one of the PPARγ subunits. Furthermore, a PPARγ agonist created seizure protection in mice (Timothy A. Simeone et al., 2017).

As a number of mitochondrial disorders are comorbid with epilepsy, mitochondrial function is also a commonly studied point in the pathology of epilepsy (Boison 2017). Through using ketones in mitochondrial energy metabolism, the ketogenic diet enhances ATP levels and metabolic enzyme levels (Rho, 2017). Enhanced energy reserves in the brain are associated with seizure protection (Sharma, 2014).

The role of polyunsaturated fatty acids (PUFAs) may also be significant in anti-epileptogenesis. PUFAs are elevated in the body during ketogenic diet treatment as a result of a high fat diet. Because PUFAs are known neuroprotective agents, they may be aiding in the anti-seizure effects of the ketogenic diet. At this time, the role of PUFAs in anti-epileptogenesis needs further assessment (Rho, 2017).

While the mechanisms of the ketogenic diet are still elusive, there are a number of hypotheses with intertwined biochemical mechanisms that may be pertinent to understanding epilepsy. The modulation of mitochondrial activity, neuroinflammation, reactive oxygen species, neurotransmitters, and ketone bodies are demonstrated biochemical agents related to ketogenic diet efficacy and antiepileptogenesis.

11.   Who does the ketogenic diet benefit most?

        The ketogenic diet is more successful for individuals with specific clinical characteristics such as age and epilepsy syndrome.

        A retrospective study at the Johns Hopkins Hospital and the Johns Hopkins All Children's Hospital was conducted in 2019 to analyze the effects of the ketogenic diet on specific epilepsies and environmental differences. Overall, 70% of individuals on the ketogenic diet had a greater than 50% decrease of seizure activity after three months on the 4:1 diet. Individuals who were more likely to achieve drug-free diet status were younger (3.8 years vs. 4.9 years). Specific epilepsies that responded more significantly to this treatment included Glut1 deficiency and Doose syndrome (myoclonic-atonic seizures). Furthermore, patients who were on fewer AEDs at the start of the ketogenic diet treatment were more likely to respond to treatment. Individuals who had Lennox-Gastaut syndrome or a gastrostomy tube were less likely to achieve drug-free seizure freedom (Lochen M. Shah et al., 2019).

        A 2010 study confirmed the improved efficacy of the ketogenic diet in a patient population with infantile spasms. Individuals who had tried fewer AEDs achieved better outcomes overall, but this result was not statistically significant ($p = 0.16$). In addition, patients who had an older age of spasm onset (0.5 years vs. 0.4 years) responded more positively to the ketogenic diet. However, this difference in age is very small and thus may not be clinically significant (Hong, 2010).

Genetic generalized epilepsies, such as juvenile myoclonic epilepsy (JME) have demonstrated especially high response rates to the ketogenic diet (Thammongkol, 2012). In addition, those with Dravet Syndrome have also responded exceptionally well. Surprisingly, patients with both genetic and acquired cortical malformations respond impressively. Patients with myoclonic-atonic seizures, Dravet Syndrome, lissencephaly, and hypoxic-ischemic encephalopathy should be initiated on the ketogenic diet as an earlier treatment option if they experience refractory seizures (Barañano, 2008).

The ketogenic diet seems to be the most promising treatment for some individuals who pose the greatest clinical challenges in epilepsy management. New-onset refractory status epilepticus (NORSE) describes a period of prolonged seizure activity with a "continuous seizure lasting for more than thirty minutes or two or more seizures without full recovery of consciousness between any of them" that is not controlled with two medications and occurs in an individual with no history of epilepsy (Ajith Cherian and Sanjeev V. Thomas, 2009). In a 2018 study, the ketogenic diet generated the highest number of positive effects in NORSE patients when compared with other antiepileptogenic therapies. Furthermore, the diet was second most efficacious out of all therapy options for patients with febrile infection-related epilepsy syndrome (FIRES), a subcategory of NORSE. It was almost five times as effective as plasmapheresis and over ten times as effective as intravenous immunoglobulins (Nicholas Gaspard et al., 2018).

Table 1: Epilepsy syndromes, conditions, and characteristics that demonstrate a probable benefit from the ketogenic diet.*

Angelman syndrome
Complex I mitochondrial disorders
Dravet syndrome
Doose Syndrome
Fewer AEDs at time of initiation
Glut-1 deficiency syndrome
Febrile infection-related epilepsy syndrome (FIRES)
Formula-fed children or infants
Juvenile myoclonic epilepsy (JME)
New-onset refractory status epilepticus (NORSE)
Ohtahara syndrome
Pyruvate dehydrogenase deficiency
Super-refractory status epilepticus
Tuberous sclerosis Complex
Younger individuals

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*Adapted from Kossoff, E. H., Zupec-Kania, B. A., Auvin, S., Ballaban-Gil, K. R., Christina Bergqvist, A. G., Blackford, R., … Practice Committee of the Child Neurology Society (2018). Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia open*, *3*(2), 175–192. doi:10.1002/epi4.12225.

12.   Limitations and Side Effects

Like any treatment for epilepsy, the ketogenic diet may create side effects that must be considered when administering the diet as a treatment. Across studies, the most common adverse effects reported involve gastrointestinal problems. Vomiting is documented especially during the diet initiation phase, while constipation sometimes occurs during the maintenance of the diet. It is not uncommon for research participants to begin a medication for constipation relief during the dietary treatment period. A small percentage of participants experience kidney stones. Because the diet lacks protein, there are significant and justified concerns about growth of young children on the ketogenic diet. However, physicians must consider that a child's growth and development may be greatly impacted by seizures, especially if the seizures occur frequently or last for minutes or longer. Depending on the individual case of each child, the benefits of age-appropriate development that occurs when seizure frequency is reduced may outweigh the potential for any growth retardation as a result of the ketogenic diet (Zupec-Kania, 2008). After the diet is discontinued, both height and weight increase appropriately (Sharma, 2014). Because the ketogenic diet is usually administered temporarily for up to two years, most children are able to reverse any decrease in growth that may occur with the diet.

Blood work and lab results also differ slightly for individuals on the ketogenic diet when compared with normal blood work profiles. Patients on the diet tend to have an increase in low-density lipoprotein and reduction in high-density lipoprotein (Zupec-Kania, 2008 and Sharma, 2014). Water-soluble vitamins, fiber, vitamin K, linolenic acid, and most minerals can be decreased (Zupec-Kania, 2008). Although serum cholesterol and triglyceride levels may

increase, they typically plateau after six months of dietary treatment (Sharma, 2014). For the

duration of the ketogenic diet, blood work should be routinely monitored.

As a type of medical nutrition therapy, the ketogenic diet has the potential to affect

growth and nutrition in the human body. While there are possible side effects of the diet that

occur in a significant number of patients, most are minor and are typically lessened throughout

the course of the treatment, or can be easily reversed.   Labs should be checked often to ensure

patient safety, optimize the antiepileptogenic effects of the diet, and minimize side effects.

13.	Alternate Uses, Benefits, and Future Directions

Still, the ketogenic diet is used increasingly in pediatric patients with refractory epilepsy.

The diet not only decreases seizure frequency, but also improves attention, alertness, concentration, and global cognition in that same population. While these outcomes in one study were subjectively reported by patients and families, alertness and adaptability significantly increased on an objective scale. This study also found that the longer that individuals were on the ketogenic diet, the more they improved in their adaptability rating, which is an "antecedent of future intelligence" (Dengna Zhu et al., 2016). Unfortunately, there are no studies that evaluate cognitive effects of the diet after discontinuation.

Because seizures can impact cognition, children with epilepsy are at risk for additional impairments due to neural disruption at a time of development. Children with epilepsy are more likely to exhibit language delays, learning disabilities, behavioral problems, and even cognitive deterioration (K. van Rijckevorsel, 2006). If seizures are long and/or frequent, these impairments can become permanent. By decreasing or eliminating seizures in children, the ketogenic diet can improve overall cognitive function.

As dietary treatments are far less common than pharmacological and surgical treatments in medicine, there is a "lack of awareness and acceptability" of the ketogenic diet amongst physicians (Sharma, 2014). However, there has been a recent increase in research and clinical use of dietary treatments for not only epilepsy but also for diseases and disorders such as autism spectrum disorder, mitochondrial diseases, Alzheimer's disease, Parkinson's disease, and even

cancer. Today, the use of the ketogenic diet is expanding in both research and clinical fields in the treatment of epilepsy and other neurological diseases.

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