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KETOGENIC DIET IN EPILEPSY

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ABSTRACT

Epilepsy is a neurological disorder in which brain activity becomes abnormal, causing seizures, sensations, and sometimes loss of awareness. Epilepsy affects both males and females of all races, ethnic backgrounds and ages. A seizure can occur when there is a disruption in the balance between the neurotransmitters in the brain, particularly due to the over-excitation of the nerves and excessive nervous messages being fired. Epilepsy usually treated with medication such as nerve pin medication, sedative & anticonvulsants and in some cases by surgery, dietary changes. The ketogenic diet (KD) is a high fat, low carbohydrate, controlled protein diet that has been used since the 1920s for the treatment of epilepsy. The CKD is rich in lipids and low in carbohydrates and protein, in order to produce ketosis, and simulates a starvation state. The ketone bodies and polyunsaturated fatty acids presumably play a major role in the anticonvulsant effect of ketogenic diet. Ketogenic diet participates in various mechanisms i.e. regulation of neurotransmitters, limiting glycolysis pathway, tri-carboxylic-acid cycle and oxidation of polyunsaturated fatty acid; induces the anti-seizures responses. But continues and very strict adherence to ketogenic diet causes some adverse effects on human body disrupting the normal mechanism of body.

KEYWORDS: Epilepsy, seizure, ketogenic diet.

INTRODUCTION

Epilepsy, one of the most common neurological diseases globally and affects people of all ages. It is characterised by 2 or more unprovoked seizure, sometimes brief episodes of involuntary movement accompanied by loss of consciousness and loss of control of bowel or bladder function. Prevalence and incidence of epilepsy varies with aetiology and seizure type. In most cases the cause remains unknown and it may result from birth defect, cerebral inflammation or tumour. Genetic mutations and homozygous variants were only identified in a small proportion of epilepsy cases.[1,2] About 50 million people (>2-3% of the population) suffering from epilepsy around world and 2 million new cases were reported each year.[2] If there is advances in the diagnosis and management of epilepsy, approximately 30% of children who develop epilepsy still experience uncontrolled seizures or intolerable side effects from AEDs. Epilepsy usually treated with medication such as nerve pin medication, sedative & anticonvulsants and in some cases by surgery, dietary changes.[2]

Ketogenic diet is high fat, low protein, low carbohydrate diet, a non pharmacological approach for treating epilepsy in those who are not treatable with antiepileptic medication and mostly useful in children.[3] Classic ketogenic diet is a strict 3:1–4:1 ratio of fats to carbohydrate and protein, some variations are developed to improve tolerability and reduce adverse effects, these include Atkins diet, low glycemic index diet, and the Medium Chain Triglyceride (MCT) Ketogenic Diet.[4] Ketogenic diets mimic the body's response to starvation and using fat as the primary energy source. Normally the body metabolizes carbohydrates into glucose and in fasting state; amino acids cannot provide adequate energy for brain. The liver uses the fatty acids to make ketone bodies, which can cross the blood brain barrier and substitute for glucose as an energy source. The mechanism controls seizures with keton body is still unknown, the theory is that ketones have an anticonvulsant effect when crossing the blood brain barrier.[5]

EPILEPSY

Epilepsy is a neurological disorder in which brain activity becomes abnormal, causing seizures, sensations, and sometimes loss of awareness. Epilepsy affects both males and females of all races, ethnic backgrounds and ages. Seizure symptoms can vary widely. Some people with epilepsy simply stare blankly for a few seconds during a seizure, while others repeatedly twitch their arms or legs. Treatment with medications or sometimes surgery can control seizures for the majority of people. Some children with epilepsy may outgrow the

condition with age. Because epilepsy is caused by abnormal activity in the brain, seizures can affect any process that brain coordinates. Signs and symptoms include temporary confusion, staring spell, uncontrollable jerking movements of the arms and legs, loss of consciousness or awareness, psychic symptoms such as fear, anxiety.[1,2]

PATHOPHYSIOLOGY OF EPILEPSY

A complex network of neurons that transmit nerve impulses and signals is evident in the brain. Neurotransmitters play an important role in the propagation of these impulses, responsible for carrying the message across the synapse of the neurons. Neurotransmitters are generally known to be excitatory or inhibitory, according to the effect they have on the firing of impulses. Glutamate is a common excitatory neurotransmitter that promotes the propagation of impulses, whereas GABA is primarily responsible for the inhibition of nerve impulses. A seizure can occur when there is a disruption in the balance between the neurotransmitters in the brain, particularly due to the over-excitation of the nerves and excessive nervous messages being fired. For this reason, typical anticonvulsant drugs tend to increase the inhibitory neurotransmitter, GABA, helping to control the frequency of seizures.[6,7]

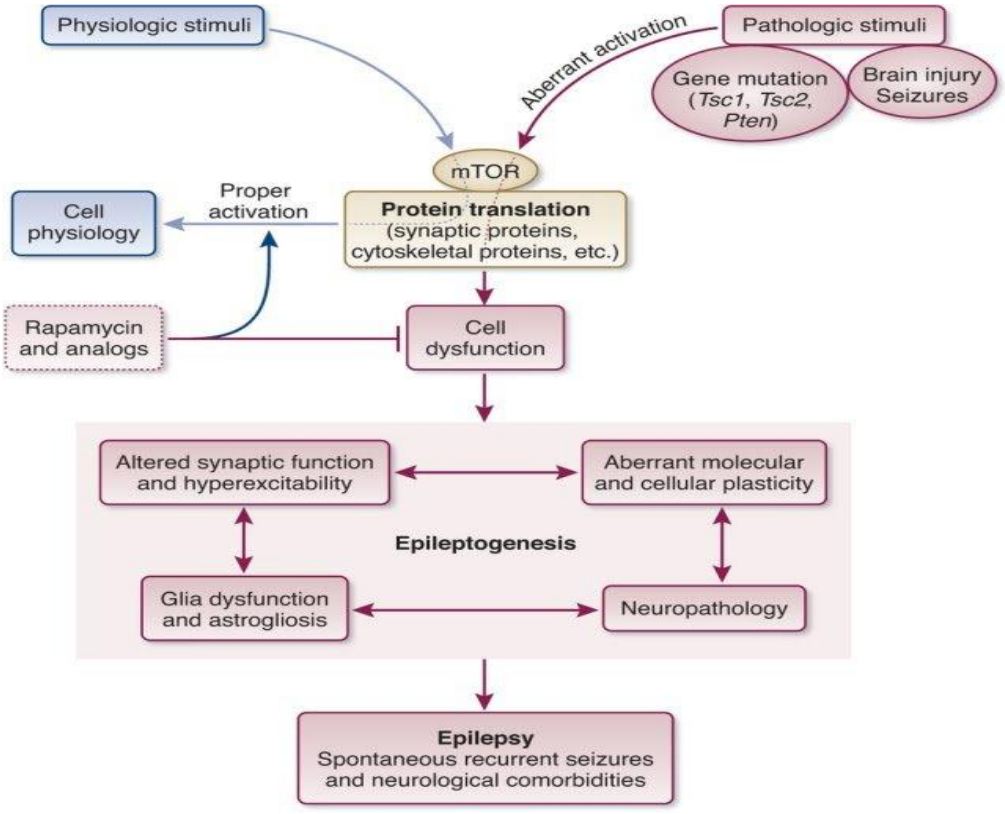

Figure (1): Pathophysiology of epilepsy.

HISTORY OF KETOGENIC DIET AND SIDE EFFECTS

Dietary treatments for diseases have probably been used for over 2000 years. Fasting is the only therapeutic measure against epilepsy recorded in the Hippocratic collection. In 1998, a multicenter study was conducted in 51 children with drug-resistant epilepsy. In that study 47% of children remained on a diet for a year, where in 43% of them was seizure-free, 39% controlled 50–90% of seizures, and 17% did not respond. Several adverse reactions associated with the administration of a ketogenic diet were occurred and includes severe dehydration or acidosis, lethargy, somnolence, severe infections, mood swings, vomiting, and constipation. The reasons for discontinuing treatment were intolerance, difficulties in maintaining a restrictive diet and inadequate seizure control.[8,9]

KETOGENIC DIET

The ketogenic diet (KD) is a high fat, low carbohydrate, controlled protein diet that has been used since the 1920s for the treatment of epilepsy. The CKD is rich in lipids (90%) and low in carbohydrates and protein, in order to produce ketosis, and simulates a starvation state. It must also provide adequate vitamins and minerals. The shift in the energy metabolism from glycolytic energy production to energy generation through oxidative phosphorylation (fatty acid b-oxidation and ketone-body production) is part of the anticonvulsant mechanism of the KD. It is stricter than the other diet requiring careful measurements of calories, fluids, and proteins. Usually the body uses carbohydrates (such as sugar, bread, pasta) for its fuel. Because the ketogenic diet is very low in carbohydrates, fats become the primary fuel instead. Ketones can be detected in the urine, blood, and breath. A ketogenic diet "ratio" is the ratio of fat to carbohydrate and protein grams combined. The kinds of foods that provide fat for the ketogenic diet are butter; heavy whipping cream, mayonnaise, and oils (e.g., canola or olive). Because the amount of carbohydrate and protein in the diet have to be restricted, it is very important to prepare meals carefully.[9] Example for ketogenic diet given in table(1)

Table (1): Example for ketogenic diet.

MEAL COMPONENTS	APPROXIMATE HOUSEHOLD MEASUREMENT
Breakfast	
Heavy whipping cream:65g Protein: 25.5g egg and 10g bacon Fat :10g butter and 13.8g mayonnaise Carbohydrate:6g peaches	2 oz heavy cream 0.5 egg and 2 strips of bacon 2.5 pats butter, 1 packet mayonnaise 1 tsp peaches
Lunch	
Heavy whipping cream:65g Protein:6.6g macadamia nuts,19.6g deli ham,8.4 g cheese Fat:10.9g mayonnaise and 4g oil Carbohydrate:10.4 g applesauce	2 oz heavy cream 2.5 macadamia nuts, 1.5 slice deli ham, 0.5 slice cheese 1 packet mayonnaise and 1 tsp oil 2 tsp applesauce
Dinner	
Heavy whipping cream:65g Protein : 25.5g egg and 10g bacon Fat:11.4g mayonnaise and 4g oil Carbohydrate:14.2g broccoli	2 oz heavy cream 0.5 egg and 2 strips of bacon 1 packet mayonnaise and 1 tsp oil 1 T broccoli

CLASSIC KETOGENIC DIET

Ketogenic Diet is the original Ketogenic Diet that was designed in 1923 by Dr. Russell Wilder at the Mayo Clinic for the treatment of epilepsy, with a 4:1 ratio of fat to protein and carbs, 90% of calories come from fat, 6% from protein, and 4% from carb. A 4:1 ratio is considered the gold-standard for classic Keto; a 3:1 ratio is also included.[9,10] This diet is also considered a low glycemic therapy and results in steady glucose and insulin levels. The diets of infants and children are the easiest to control so they started on the more restrictive Classic Keto diet.

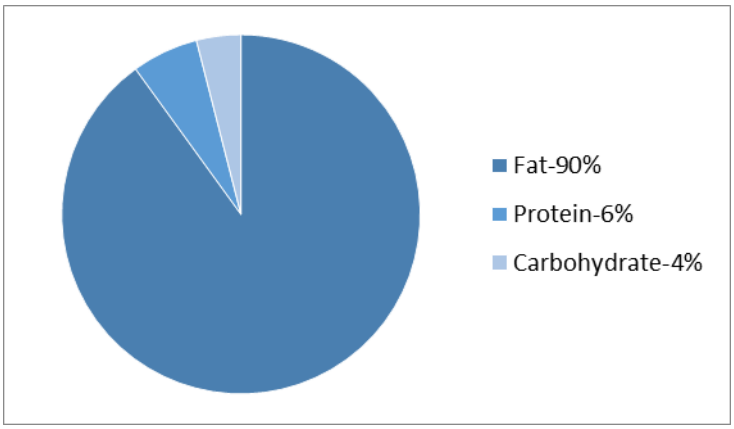

Figure (2) Classic ketogenic diet ratio.

MEDIUM CHAIN TRIGLYCERIDE KETOGENIC DIET

The Peter R. Hutten ocher MD is created the medium chain triglyceride (MCT) ketogenic diet in the 1970s. Its various versions are used in centers across the United Kingdom and Europe. The MCT ketogenic diet uses a fat supplement that consists only of MCT fats. It includes medium chain triglyceride fats like coconut oil.[10]

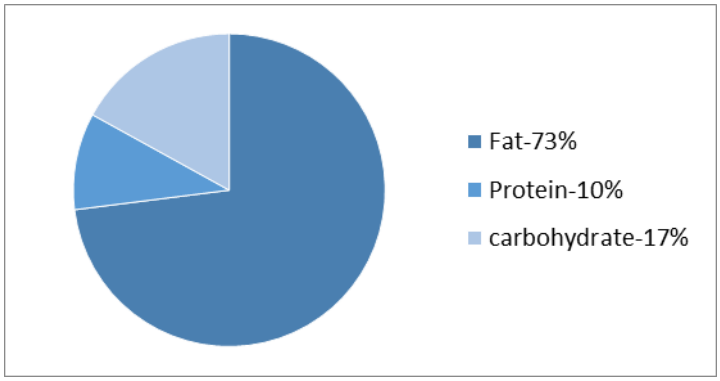

Figure (3) MCT KD ratio.

ATKINS DIET

Atkins diet was created by a physician at John Hopkins named Dr. Robert C. Atkins in 1972. Here weighing of food is not required, and, total carbs per day is generally limited to 10-20 grams. It limits carbohydrate intake and allows the protein as much as the eater desires. It is usually initiated in an outpatient setting, though the person must still be monitored to ensure safety. It is often used as a transition onto or from a more strict Ketogenic Diet, as well as for families lacking resources necessary to administer a more restrictive Keto plan.[10]

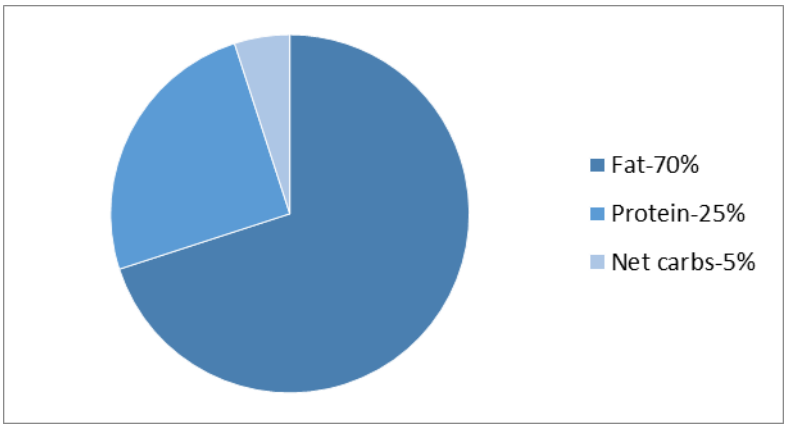

Figure (4) Atkins diet ratio.

ANTI-SEIZURE MECHANISMS OF THE KETOGENIC DIET

The ketone bodies and polyunsaturated fatty acids presumably play a major role in the anticonvulsant effect of ketogenic diet. During ketogenic diet treatment, body energy is generally generated by the oxidation of fatty acids in mitochondria, resulting in the production of large amounts of acetyl-CoA. Accumulation of acetyl-CoA leads to the synthesis of two ketone bodies mainly in the liver, acetoacetate, and β-hydroxybutyrate, which then enter the blood circulation. Ketone bodies are then used as an alternative source of energy in the brain instead of glucose.[6] After entering the brain, the ketone bodies are transformed into acetyl-CoA and then enter the tricarboxylic acid cycle in the mitochondria of the brain, which ultimately leads to the production of adenosine triphosphate (ATP). Several hypotheses regarding ketone bodies are considered as key mediators involved in the anticonvulsant effect of the ketogenic diet. Based on several studies, potential mechanisms focus essentially on the role of neurotransmitters, brain energy metabolism, oxidative stress, and ion channels showed in figure(5). Energy production in the brain is significantly increased by ketogenic diet. Long term ketogenic diet lead to increased expression of energy metabolism gene, improves mitochondrial biogenesis and density and increases energy reserves in the form of phosphocreatine.

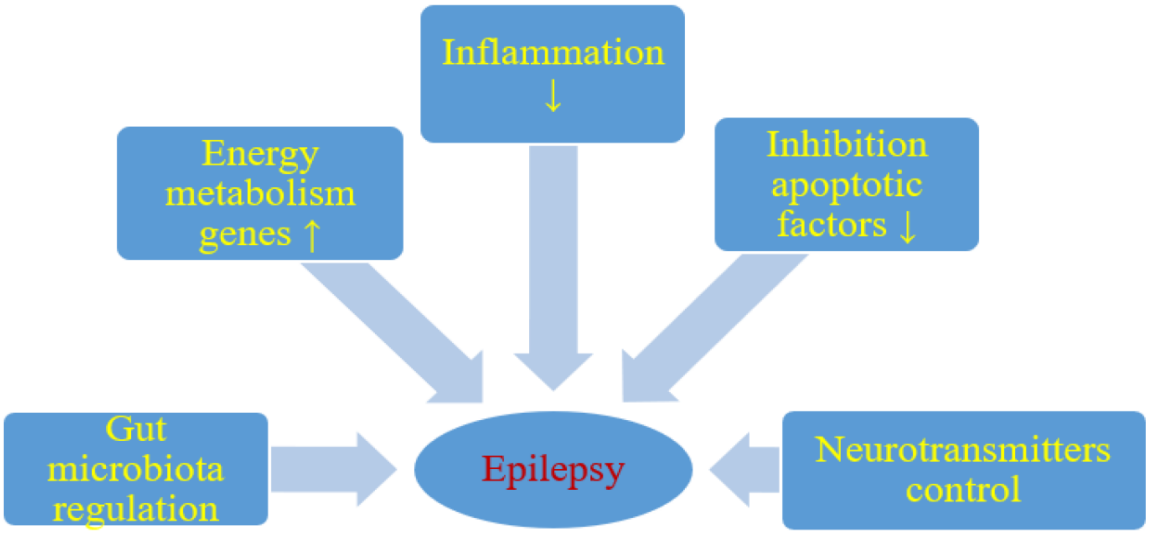

Figure (5) Effect of ketogenic diet on epilepsy.

Reduction of neuronal excitability is the most important role of GABA in the brain and therefore GABA plays a key role in the initiation and spread of seizure activity in the brain. It has been observed that ketogenic diet can lead to glutamic acid decarboxylase activation, which induces GABA synthesis.[7] It has also been shown that this diet can alter GABA

transaminase activity that inhibits GABA degradation. Increasing energy metabolism through a ketogenic diet can compensate for the metabolic and transient failure of GABAergic inhibition, the lack of which will not prevent the occurrence and spread of seizures. Therefore, another important mechanism induced by the ketogenic diet in anticonvulsant activity is probably mediated by the GABAergic system.

Agmatine has been found in synapses and can be considered as an inhibitory neurotransmitter. It may exert an anti-seizure effect, probably by inhibiting various brain stimulating receptors, including N-methyl-D-aspartate, histamine, and adrenaline receptors. It has been shown in rat studies that ketogenic diet can increase the level of agmatine in the hippocampus.[11] The above observations support the view that the ketogenic diet increases the level of agmatine in the brain, which has neuroprotective properties, therefore these properties can be considered as another anticonvulsant mechanism of the ketogenic diet.[11,12]

KETOGENIC DIET IN OTHER NEUROLOGIC ILLNESS

Metabolic defects

The utility of the ketogenic diet in PDH deficiency and GLUT-1 deficiency likely derives from its ability to provide 2-carbon substrates, with subsequent relief of blocks in metabolism upstream from the tricarboxylic acid cycle.[13]

The ketogenic diet also has been used in glycogenosis type V, which is caused by a defect in the muscle-specific isozyme of glycogen phosphorylase. Glycogen phosphorylase is necessary to break down glycogen into free glucose for use as an energy source in muscles. When the ketogenic diet was applied to a patient with this disorder, the patient's exercise tolerance improved and there was a trend toward decreased baseline creatine kinase levels.

Malignancy

The ketogenic diet may have a role in treating disorders of cellular proliferation, especially cancer. Here normal tissue can adapt readily to using ketones (instead of glucose) as a substrate, but malignant cells probably do not have the same degree of metabolic flexibility. One case report in 1995, described the use of the ketogenic diet in two girls with advanced astrocytomas, based on the idea that brain tumors are less able than healthy brain tissue to use ketones as an energy source. In this report, PET studies demonstrated a 20% reduction in glucose uptake by the tumors following the initiation of the ketogenic diet. One of the patients actually showed improvement during the course of the study and has continued to be

well, without evidence of tumor progression. Ketogenic diets have been associated with decreased tumor growth in animal models of gliomas, prostate cancer, and gastric cancer.[14]

Trauma and ischemia

Animal data suggest a role for the ketogenic diet in protection against trauma and ischemia, as ketones may be a preferred fuel in the injured brain.[14,15] The role of the ketogenic diet in a controlled cortical impact model in rats. Young rats of varying postnatal ages underwent a small craniotomy and then, with the dura intact, were subjected to a standardized piston cylinder injury. Immediately after the impact, the rats started a standard diet or the ketogenic diet. After 1 week, a post-mortem measurement of cortical contusion area was performed. The contusion area was significantly decreased in postnatal day-35 and day-45 rats that had been fed the ketogenic diet, but not in younger or older rats.[15]

Neurodegenerative disorder

In the case of Parkinson's disease (PD) and Alzheimer disease (AD) models, there are data suggesting that calorie restriction itself is protective. The ketogenic diet originally was designed to mimic fasting, and thus it may regulate a family of proteins known as sirtuins, which play a major role in mediating "anti-aging" effects of calorie restriction. The ketogenic diet may regulate a master energy-sensing protein in the cell, 5′-adenosine monophosphate (AMP)–activated kinase.[16] Both proteins have a number of downstream effectors that may possess neuroprotective properties. Finally, with its low carbohydrate content, the ketogenic diet's impact on glucose use and factors such as brain-derived neurotrophic factor may be important.[17,18]

CHALLENGES IN ADHERING TO KETOGENIC DIET

- The fasting and dietary changes are affected by cultural and religious practice.
- When the food is prepared by a family member other than parents, they must be well educated about the preparation of the diet.
- When the family members are eat together, it may be too difficult to isolate the patients meal.[1]
- In many countries, the food labelling is not mandatory. Hence the calculation of fat, protein and carbohydrate is very difficult.[19,20]

CONCLUSION

Composition of ketogenic diet includes highest ratio of fat, moderate ratio of protein and lowest ratio of carbohydrate. Combination of energy giving nutrients in this ratio induces the ketosis which leads to reduction in the initiation of seizure. The ketone bodies and polyunsaturated fatty acids presumably play a major role in the anticonvulsant effect of ketogenic diet.

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