Review

Management of Epilepsy with Ketogenic Diet

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Abstract

Intractable epilepsy has been defined as epilepsy that failed to respond to 3 or more anti-epileptic drugs (AED). About 30% of children with epilepsy experience uncontrolled seizures or side effects due to AED [1]. The ketogenic diet (KD) was found to be effective in treatment of intractable seizures. The KD consists of a high fat, low carbohydrate and adequate protein. The KD need to be tailored individually for every patient. Different protocols and variable dosing of KD have been used. The KD is prescribed by physician and dietician, thereafter side effects such as acidosis, hypoglycemia, vomiting, gastro-esophageal reflux, constipation, hyper-lipidemia, renal stone, growth failure, bone density, micro-nutrient and vitamin deficiency need to be monitored.

Introduction

Fasting has been recognized since Hippocratic era (460BC-370BC) as treatment for epilepsy. In early 20th Century, French and American physicians like Guelpa, Marie, Conklin, and Geyelin started research on fasting and starvation as treatment for epilepsy [1]. It was shown that the fasting is more effective more in treating children than adolescents and its efficacy decreases with increasing age. Thereafter, Lennox and Cobb (1922) explained dehydration, acidosis, and ketosis as possible mechanism by which fasting helps in treating epilepsy.

Dr. Wilder proposed that the diet which produces ketosis could also be used in treatment of epilepsy. He termed such diet as "Ketogenic Diet", which were rich in fat and deficient in carbohydrate. He found benefit of KD over starvation in providing similar efficacy, but can be used for prolonged maintenance.

Later, in 1938 diphenylhydantoin was discovered and thereafter research focus shifted to development of other AED, which were found convenient to administer.

Due to intractable seizures which remained uncontrolled despite of several trial of AEDs, KD regained its popularity. In 1972, Dr. Robert C. Atkins promoted "Atkins Diet" which consisted of high fat and low carbohydrate and produces ketosis. Thereafter, "Modified Atkins Diet" was developed in 2003 at John Hopkins. These diets were more palatable and tolerable than previous ones.

Subsequently, low glycemic index treatment diet was proposed in 2005, which hypothesis that stable blood glucose at a lower level would result in modulation of

insulin release and other metabolic effects, thus improving seizure.

Mechanism of Action

The exact mechanism of action of ketogenic diet is still not fully clear. However, preclinical studies have suggested following possible mechanism as alterations in mitochondrial function, effect of ketone bodies and fatty acids, and glucose stabilization. Ketone bodies easily cross the blood brain barrier, and are only source of energy to brain during starvation. Substitution of glucose by ketones in brain results in decreased glycolysis and increased krebs cycle for energy production. Ketone bodies causes γ-aminobutyric acid (GABA) synthesis, neuronal membrane hyperpolarization, decrease release of glutamate, increase norepinephrine and adenosine, neuroprotective and antioxidant activity, decrease insulin-like growth factor 1 (IGF-1) and the mammalian target of rapamycin (mTOR), and increase sirtuins and adenosine monophosphate-activated protein kinase (AMPK) in

brain. The GABA is synthesized during krebs's cycle when glutamate is converted into GABA by enzyme glutamate decarboxylase. Studies have shown that beta-hydroxybutyrate (ketone body) inhibits GABA-transaminase expression thus increases GABA in brain. Ketone bodies regulates activity of these enzyme thus increases the level of GABA in the brain. Increased level of GABA results in stimulation of chloride receptors and ATP sensitive potassium channel leading to hyperpolarisation of neuronal membrane and inhibition of sodium and calcium channels leading to decreased excitability. Studies have shown ketone bodies (acetoacetate more than betahydroxybutyrate) affect VGLUT channels on presynaptic glutamate vesicles (via chloride channels), thus leading decreased release of excitatory glutamate neurotransmitters. Ketone bodies also cause alteration in level of biogenic amines such as increase in nor-epinephrine and adenosine, and decrease in dopamine and serotonin. Increased adenosine causes activation of adenosine A1 receptors resulting in decreased brain excitability. Ketone bodies have neuroprotective role by causing mitochondrial biogenesis. It also have antioxidant role by increasing uncoupling protein in mitochondrial electron transport chain thus reducing reactive oxygen species and increasing level of mitochondrial reduced glutathione level thus protecting mitochondrial level from oxidative stress. Increase in sirtuins causes increase in mitochondrial number and size, and also cause decrease in insulin like growth factor-1. Increase in AMPK is directly related to ATP production. Ketone bodies by inhibiting mTOR pathway have anticonvulsant action. Since ketone bodies metabolizing enzyme (namely, monocarboxylic acid transporter) is found more abundant in infants and children, which later decreases with increasing age and adults. Therefore the KD is more effective during infants and childhood than in adulthood [2].

The Classical Ketogenic Diet

Most of classical ketogenic diet consist of higher fat than carbohydrate and protein, in such a ratio that the ratio of quantity of fat and the sum of quantity of carbohydrate and protein is in range of 3:1 to 4:1. Therefore, 90% of the total calories delivered in KD is by fat and the remaining 10% is by carbohydrate and protein. The total calories is restricted to 80 to 90% of daily recommendation for the age and the fluid restriction is 90% of previous dietary intake. The KD is preferably started after admitting patient in hospital. Whereas, out-patient setting is not a contraindication, in-door setting has several advantages as it provides better opportunity to thoroughly examine and evaluate the case for diagnosis and contraindications of KD, provide education session for parents about KD preparation and administration, monitoring of side effects, and also some centers initiate 4:1 preparation of classical KD after brief fasting to provide accelerated ketosis. However, gradual initiation of KD is better tolerated, lesser side effects, similar level of maintenance ketosis, and similar level of seizure control compared with fasting KD initiation. Therefore, gradual initiation of KD should be preferred over fasting KD initiation. During gradual initiation, initially 2:1 combination of KD is started which is later increased to 3:1 and 4:1 based on tolerability [2]. Most of patients respond well to one year treatment with KD, averaging about 80% response rate. Among responders, more than 50% response is noticed in initial 3 months, and among those with less than 50% response in initial 3 months, not much improvement is noticed thereafter. The average time for treatment with KD is 2years after which it may be discontinued [2]. As a clinical practice, usually KD is used as a reserved therapy for intractable seizures. The International Ketogenic Diet Study Group, the therapy should be offered after failure of two AED trial. However, KD remains treatment of choice for GLUT1 deficiency syndrome and pyruvate dehydrogenase deficiency syndrome. Whereas, for Dravet Syndrome (myoclonic epilepsy of infancy) and Doose Syndrome (myoclonic-atonic epilepsy), Infantile Spasm/West Syndrome, Lennox Gestaut Syndrome, KD have been found more effective and hence can be considered earlier. The adverse effects reported for KD are unpalatability, taste change, nausea, vomiting, abdominal pain, constipation, diarrhea, infection, dehydration, hunger, lack of energy, mood changes. Pancreatitis though rare but serious and found in

association with triglyceridemia among patients on KD. Other long term complications are growth retardation in children, electrolyte, vitamins, and mineral deficiency, hyperlipidemia, nephrolithiasis [3].

The KD is contraindicated in patients with disorder of disorders of fatty acid transport and oxidation. Therefore, developmental delay, cardiomyopathy, hypotonia, exercise intolerance, myoglobinuria, and easy fatigability are few features that should raise high suspicion of fatty acid metabolism disorder, and patients with such feature should undergo screening test for inborn error of metabolism before initiation of KD therapy. The use of KD with valproate may cause liver failure. The studies on efficacy of KD have been summarized in table 1.

Study	Findings
Vining et al. 1998 [4] 51 children with average 230 seizures/month.	Continued treatment for a year: 47% Efficacy in terms of seizure control after 1 year treatment: >90% response – 43%; 50-90% response – 39%; <50% response – 17% Adverse effects: lethargy, severe dehydration, acidosis, mood changes, increased infections, constipation, and vomiting. Reason for discontinuation: intolerance, difficulty of maintaining the restrictive diet, and inadequate seizure control.
Freeman et al. 1998 [5] 150 children with average 410 seizures/month.	Efficacy in terms of seizure control after 1 year treatment: 100% response - 7%; >90% response - 27%; 50-90% response - 50% More than 50% improvement in initial 3 months responded well, whereas less than 50% response in initial 3 months did not had much improvement later.
Freitas et al. 2007 [6] 70 children with refractory epilepsy	Continued treatment for a year: 55% Efficacy in terms of seizure control after 1 year treatment: >75% response - 70%; 75-25% response - 25%; <25% response – 2.5% Reason for discontinuation: unpalatability, nausea, and vomiting More effective for generalized epilepsy than for partial epilepsy

Neil et al. 2008[7] Randomised Controlled Trial on 103 children with refractory epilepsy	Efficacy in terms of seizure control after 3 months of treatment: KD Group (n = 54) had 75% reduction in seizure frequency compared to Control (AED) Group (n = 49). 90% response – 7%; 50-90% response – 38% Adverse effect: Constipation, vomiting, lack of energy, hunger, diarrhea, abdominal pain, and taste problems among 25% KD Group.

Table 1: Summary of studies on efficacy of Ketogenic Diet.

The Medium Chain Triglyceride (MCT) Diet

Since unpalatability was one of the major reason for discontinuation of use, MCT diet limited this adverse effect to some extent with a greater proportion of carbohydrate and protein content than KD. The MCT diet are more rapidly metabolized compared to long chain triglycerides in classical KD, therefore has several advantages over classical KD. It produces more ketosis per kilocalorie of energy and requires lesser amount of fat intake than classical KD. It also has lesser total cholesterol to high density lipoprotein ratio compared to classical KD. Although, it has adverse effects as diarrhea, vomiting, bloating, and abdominal pain. Therefore to reduce these adverse effects, the modified MCT diet have been developed. Instead of providing 60% total energy with MCT diet, the modified MCT diet provides 30% of energy with MCT and 30% energy with long chain triglycerides. However, contraindications for MCT diet are almost similar to KD.

The Modified Atkins Diet (MAD)

The MAD in composed of fat, protein , and carbohydrate is a ratio such that 60-65% calories is delivered by fat, 30% by protein, and the remaining 10% by carbohydrate. For children, the net carbohydrate are initially limited to 10 g/day which is later on increased to 20 g/day, whereas in adults the initial carbohydrate dose is started at 15 g/day which is later on increased to 20-30 g/day. Goal of MAD is to increase the ketosis without causing weight loss, therefore only carbohydrate consumption is restricted but fat and protein consumption is encouraged. There is no fasting required, calories are not restricted, weighing of food is not required, lesser education to family members and patient required and can be safely started at home.

Study	Findings
Sharma et al. 2013 [8] Randomised controlled trial comparing MAD and AED on 102 children and adolescents with refractory epilepsy.	Efficacy in terms of seizure control after 3 months of treatment: MAD Group (n= 50) had significant reduction in seizure frequency compared to Control (AED) Group (n = 52). The MAD was well tolerated and did not required discontinuation, though constipation was most common side effect.

Table 2: Summary of study on efficacy of Modified Atkins Diet.

The Low Glycemic Index Treatment (LGIT)

The low glycemic index (GI) food has lesser tendency to elevate postprandial blood sugar level. The food with GI less than 50 is preferred, with total carbohydrate 40-60 g/day initially, however, fat and protein is encouraged. The LGIT produces lower level of ketosis than the classical KD. The key findings of studies on efficacy is summarized in table 3.

Study	Findings

Muzykewicz et al. 2009 [9] 76 children with refractory epilepsy	Efficacy in terms of seizure control after 1 year treatment: >50% response - 66% Only 3 patients reported transient lethargy as side effect. Most common reason for discontinuation was restrictiveness.
Coppolla et al. 2011 [10] 15 children and young adults with refractory epilepsy	Efficacy in terms of seizure control after 1 year of treatment: 75-90% response - 40%; 50% response - 13%; <50% response – 47% No adverse effect reported.

Table 3: Summary of studies on efficacy of Low Glycemic Index Treatment.

Study	**Findings**
Neal et al. 2009[11] Randomised controlled trial comparing MCT and classical KD.	No difference among efficacy of the MCT diet (n = 49) and the KD (n = 45).
Martin et al. 2016 [12] Cochrane review of 7 Randomised Controlled Trial among children and adolescents with epilepsy.	Efficacy of classical KD: 85% seizure reduction and 55% seizure free. Efficacy of MAD: 60% seizure reduction and 10% seizure free. Gastrointestinal symptoms (diarrhoea, constipation and vomiting) were among most commonly reported side effects, and also one of the most common reason for discontinuation. Whereas, cardiovascular adverse effects were among most common long term side effects. Classical KD had greater side effects.
Klein et al. 2014 [13] Review of studies on KD and MAD among adults with refractory epilepsy.	Efficacy of classical KD: >50% response – 32% and >90% response –9%. Efficacy of MAD: >50% response – 29% and >90% response –5%. Side effects of both diets are benign and similar. The most common being weight loss and most serious being reversible hyperlipidemia. Refusal to participate because of diet restrictiveness and complexity is more for KD than MAD. Also, discontinuation rate is more among KD (51%) than MAD (42%).

Ye et al. 2015 [14] Meta-analysis comparing efficacy of KD (n = 168), MAD (n = 87), MCT + KD (n = 15) among 270 adults with intractable epilepsy.	The KD (52%) had significantly higher efficacy than MAD (34%). The overall compliance rate of KD(38%) was significantly lower than MAD (56%). Due to better compliance rate MAD may be initial treatment of choice for adults, which may be switched to classical KD if greater seizure control is desired.

Table 4: Comparing of efficacy of Ketogenic Diet with newer variants.

Conclusion

Though, the classical KD is proven treatment for intractable epilepsy, the newer diet have been developed in order to reduce the side effects and making it more palatable for prolonged maintenance use. Despite having fewer side effects and better tolerability, the studies have found these newer diets to be comparably effective as the classical KD (Table 4). Based on understanding about mechanism of ketogenic diet, the recent researches are focusing to develop newer dietary alternatives eg. pyruvate, triheptanoin, alpha-ketoglutarate, succinate, oxaloacetate supplementation. The development of future diet for epilepsy may reduce side effects of classical KD and increase palatability, tolerability, and compliance.

References

1. *Sampaio LP de B. Ketogenic diet for epilepsy treatment. Arq Neuropsiquiatr. 2016;74(10):842–848.*
2. *Lima PA de, Sampaio LP de B, Damasceno NRT. Neurobiochemical mechanisms of a ketogenic diet in refractory epilepsy. Clinics. 2014;69(10):699–705.*
3. *Vaccarezza MM, Silva WH. Dietary therapy is not the best option for refractory nonsurgical epilepsy. Epilepsia. 2015;56(9):1330–1334.*
4. *Vining EPG, Freeman JM, Ballaban-Gil K, Camfield CS, Camfield PR, Holmes GL, et al. A Multicenter Study of the Efficacy of the Ketogenic Diet. Arch Neurol. 1998 Nov 1;55(11):1433–7.*
5. *Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, others. The efficacy of the ketogenic diet—1998: a prospective evaluation of intervention in 150 children. Pediatrics. 1998;102(6):1358–1363.*
6. *Freitas A, Paz JA da, Casella EB, Marques-Dias MJ. Ketogenic diet for the treatment of refractory epilepsy: a 10 year experience in children. Arq Neuropsiquiatr. 2007 Jun;65(2B):381–4.*
7. *Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7(6):500–506.*
8. *Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. Epilepsia. 2013;54(3):481–486.*
9. *Muzykewicz DA, Lyczkowski DA, Memon N, Conant KD, Pfeifer HH, Thiele EA. Efficacy, safety, and tolerability of the low glycemic index treatment in pediatric epilepsy. Epilepsia. 2009;50(5):1118–1126.*
10. *Coppola G, D'Aniello A, Messana T, Di Pasquale F, della Corte R, Pascotto A, et al. Low glycemic index diet in children and young adults with refractory epilepsy: First Italian experience. Seizure. 2011 Sep;20(7):526–8.*
11. *Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia. 2009;50(5):1109–1117.*
12. *Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Libr [Internet]. 2016 [cited 2017 Feb 11]; Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001903.pub3/pdf*
13. *Klein P, Tyrlikova I, Mathews GC. Dietary treatment in adults with refractory epilepsy A review. Neurology. 2014;83(21):1978–1985.*
14. *Ye F, Li X-J, Jiang W-L, Sun H-B, Liu J. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. J Clin Neurol. 2015;11(1):26–31.*