Ketogenic diet

Update and application

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ABSTRACT

The ketogenic diet is a high-fat, low-carbohydrate, and adequate-protein diet for the treatment of intractable seizures in children, initially introduced in 1921 to mimic the biochemical changes associated with fasting. The diet is individually calculated and rigidly controlled, requiring a comprehensive medical team approach. Although there are adverse, as well as, beneficial effects, several studies have proved its tolerability and efficacy in children with medically refractory epilepsy. Children must be carefully selected, monitored, and followed, and the parents must be committed. The division of Pediatric Neurology at King Faisal Specialist Hospital & Research Center in Jeddah is one of very few centers that provide this treatment option in the Middle East. Over the last 2 years, 8 children with intractable epilepsy were placed on the ketogenic diet in our center. Overall, 38% (3/8) reached accepted efficacy (>50% seizure reduction), which is lower than the 50% efficacy in published literature. Many issues and problems arose in the provision and compliance with the ketogenic diet, many of which were unique to our culture. It is critical that this treatment is provided to highly selected children with committed parents.

Despite the advances in antiepileptic drug (AED) development, 25-30% of epileptic patients remain intractable.[1] Intractability is considered if patients have at least one seizure every 2 months and have tried at least 3 AEDs.[2] Non-pharmacological treatment options available for these patients include epilepsy surgery, vagus nerve stimulation, and the ketogenic diet. The ketogenic diet is a high-fat, adequate-protein, and low carbohydrate diet designed to mimic many of the biochemical changes associated with prolonged starvation. In this paper, we present an updated overview of the ketogenic diet, and summarize our 2-year experience at King Faisal Specialist Hospital & Research Center in Jeddah, Kingdom of Saudi Arabia.

Historical perspective. Dietary measures have been described for the treatment of epilepsy since Biblical times. In 1911, a report from France documented the success of fasting in the treatment of epilepsy. In 1921, Geyelin[3] made the earliest scientific observations about the relationship between fasting and seizures. Later that same year, it was postulated that the antiepileptic effect of starvation resulted from ketosis.[4] Therefore, an actual diet severely limited in carbohydrate and protein was introduced at the Mayo clinic. The diet was used as a common treatment for epilepsy, along with bromides and phenobarbital, until 1930 when its popularity declined after the introduction of phenytoin. Despite the discovery of more AEDs, which was made possible by an increased understanding by researchers of the biochemical and physiological pathogenesis of epilepsy, 25-30% of patients with epilepsy remain intractable. By 1990, wide spread media attention re-awakened interest

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in the diet, after successful treatment of a child with intractable epilepsy at the Johns Hopkins Hospital.[5] Currently, the diet is an established therapeutic option for children with intractable epilepsy.

Mechanism of action. On the ketogenic diet, the brain utilizes fat rather than glucose as the primary cerebral energy source. Administration of the ketogenic diet leads to major changes in the basic biochemistry and physiology of the central nervous system. However, it is difficult to determine which of these changes is actually responsible for its efficacy. Several theories have been proposed as follow:

1. Acidosis. Acidosis decreases neuronal excitability and seizure susceptibility by decreasing sensitivity of specific subtypes of glutamate receptors[6] and decreasing gap junction coupling.[7] However, many investigators failed to document that ketosis causes any change in cerebral pH.[8] Minimal degree of intracellular acidosis with the medium chain triglycerides (MCT) version of the diet has been found.[9]

2. Ketone bodies metabolism and ketosis. Earlier studies did not elicit a relationship between the degree of ketosis and the level of seizure control.[10] However, the effects of different ketone bodies may vary. Acetoacetate and acetone reduced seizures in susceptible mice, but ß-hydroxybutyrate did not.[11] Intraperitoneal injection of acetone suppresses seizures in multiple epilepsy models; however, elevated brain acetone is not the main mechanism for seizure control.[12] Ketone bodies are metabolized through the tricarboxylic acid (TCA) cycle. Ketone bodies metabolism in the brain leads to changes in glutamate metabolism.[13] Oxaloacetate is consumed in one of the TCA cycle steps; therefore, less will be available for the transamination of glutamate to aspartate, leaving an increased pool of glutamate available for the synthesis of both GABA and glutamine. Evidence from animal studies revealed reduction of aspartate and transamination of glutamate in the brain on the ketogenic diet.[14] During ketosis, the acetate level increases in the brain causing increased production of glutamine. Finally, there is evidence of increased inhibitory synaptic transmission, mediated by GABA receptors.[15] However, direct measurements have failed to detect elevated levels of GABA in the brain of animals on the diet.[8,16]

3. Changes in energy state of the neuron. Ketosis leads to an increased ratio of ATP to ADP in the brain, which increases the activity of the ATP-dependent sodium pumps found in neuronal and glial membranes. This will result in hyperpolarization (decreased neuronal excitability) and increased glutamate uptake.[17]

4. Calorie restriction. Calorie restriction will decrease blood glucose, which will reduce the glycolytic energy available for seizures.[18]

5. Increased plasma lipids. Children on the ketogenic diet have elevated serum polyunsaturated fatty acids levels.[19] These free lipids have been shown to have antiepileptic properties.[20]

6. Neuroprotective effects. Earlier diet initiation soon after the epileptogenic stimulus, results in more effective seizure control.[21] The diet decreases the production of oxygen free radicals, enhances the activity of mitochondrial uncoupling proteins, and increases the level of glutathione peroxidase, which results in an antioxidant effect.[22] Without regard to the specific mediators, the effects of the diet on the electrophysiological properties of the brain have been investigated both in vitro and in vivo with conflicting results. In vitro, the diet did not alter baseline synaptic transmission and excitability; however, in vivo, the diet did increase the inhibition in the dentate gyrus.[23]

Types of ketogenic diet. *1. Classical ketogenic diet.* This is the most commonly studied diet with the most favorable results. It is very restrictive and requires meticulous calculations, monitoring, and family motivation and support. The classical diet contains a ratio of 4 grams of fat to each gram of protein and carbohydrate combined. A ratio of 3:1 is preferred in children under 18 months of age. The desired energy intake is 75% of recommendation for age, and the protein content is 1g/kg/day. Each meal has the same balance of fat, protein, and carbohydrate. Children on this diet may have slowed height or weight velocity, if caloric requirements are underestimated. However, a compensatory growth spurt occurs once the diet is discontinued.

2. MCT oil diet. Medium chain triglycerides (MCT) have been shown to be more effective in reducing seizures at lower quantities than long chain fats.[24] The MCT diet is calculated using 100% of the recommended daily energy intake for the child's age and size (as compared to 75% for the classical diet). Sixty percent of the total energy is derived from MCT. The remainder is distributed among saturated fat, carbohydrate, and protein. This reduced amount of fat allows greater flexibility in the choice of foods. However, the diet is not very palatable, tasteless, and difficult to swallow. Gastrointestinal distress, in the form of abdominal pain and diarrhea, may limit the use of this form of the diet.

3. Modified MCT version diets. This regimen was developed to overcome the practical difficulties of the MCT dietary calculations. Only 30% of the daily energy intake is provided from MCT. It is often incorporated in the classical ketogenic diet for a

variety of reasons, including increasing the protein and carbohydrate allowances while maintaining adequate ketosis, countering constipation, and improving dyslipidemia.

Treatment protocol. Providing the ketogenic diet requires a team approach that includes a neurologist, specialized nurses, specifically trained nutritionist, and pharmacists. Knowledge about the carbohydrate content of medications is mandatory. In addition to intractable epilepsy, the ketogenic diet is used in the treatment of children with glucose transporter deficiency and pyruvate dehydrogenase deficiency. Absolute contraindications include pyruvate carboxylase deficiency, organic aciduria, mitochondrial disorders, fatty acid oxidation problems, and carnitine deficiency.

Initiation. The ketogenic diet should be initiated gradually during a 3-5 day hospitalization following a 24-48 hour fast and fluid restriction (caffeine and sugar free). Some data showed that the initial fast may not be necessary.[25] Ketosis can be achieved, and the diet can be initiated at home. However, initial hospitalization is highly advisable to observe potential side effects of fasting, such as hypoglycemia, vomiting, and dehydration. The admission period can be used for optimal family education and medication adjustments. The initial fast can be encouraging to the family if immediate seizure control occurs.[26] Fasting is continued with 20% fluid restriction. Blood glucose should be monitored every 6 hours and hypoglycemia corrected if symptomatic or if blood glucose drops below 25mg/dl. Urine ketones should be checked by dipstick with every void. Once urinary ketones reach 3+ to 4+ (80-160 mg/dl), the diet can be started. Some authors suggested that seizure control correlates better with serum ß-hydroxybutyrate than with urinary ketones.[27] More recently, breath acetone was found to be useful in examining the relation between ketosis and seizures control.[28] In practice, urine ketones are the easiest and least expensive method of monitoring ketosis. The diet is started at a ratio of 4:1 of fat to protein and carbohydrate. The exact dietary components are calculated according to age, weight, height, and activity level. The protein component is based on the protein requirements for age and size. Carbohydrate intake is typically 5-10 g/day. The targeted total caloric intake is typically 75% of that recommended for age. Three daily meals and a snack are provided. However, a ready made liquid formula is also available for young infants or patients fed by nasogastric tubes or gastrostomy. One third of the calculated total calories is given on day one, followed by 2/3 on day 2 and full-calories afterward as tolerated.

Maintenance. Patients are discharged home on the full diet in addition to multivitamins and calcium supplements. Urine ketones should be checked several times per week, and the diet slowly adjusted to maximize seizure control. Follow-up should be monthly to monitor body weight, height, and compliance. The dietitian should adjust the caloric content, and the ratio to maximize ketosis and minimize hunger and undesired weight changes. More frequent contact can be via telephone or e-mail. Laboratory studies are performed at base line and then every 3-6 months, including blood count, lipid profile, electrolytes, renal, liver function tests, and beta hydroxybutyrate. Once the seizures are controlled, AEDs can be tapered slowly.[29] If the seizures continue, one must be sure that there are no additional carbohydrates taken from unknown sources. If urine ketones are less than 4+, a 24-hour fast with clear liquids improves ketosis rapidly. The diet should be maintained for at least 3 months to assess the seizure outcome.

Discontinuation. The ketogenic diet can be discontinued following 2 years of seizure control. Intolerable side effects, poor compliance, or lack of efficacy, are the main reasons for premature discontinuation. Gradual weaning is suggested by lowering the ratio to 2:1 and followed by increasing the portions of foods. Finally, introducing more carbohydrates and substituting whole milk by 2% and then 1%, is recommended as ketosis drops.

Side effects. The ketogenic diet can cause constipation and worsening of gastro-esophageal reflux. The MCT diet may be complicated with diarrhea and abdominal cramps. Minor diet adjustments, stool softeners, and replacement fluids can overcome these gastrointestinal side effects. Nausea and vomiting related to diet initiation or the degree of ketosis, can be managed by reducing the number of meals and replacement fluids. The family has to be educated to recognize signs and symptoms of acidosis, particularly at diet initiation or during acute illness. This is usually managed with carbohydrate-free fluids. Monitoring growth and nutritional status are mandatory as children on the ketogenic diet may show growth delay, particularly infants and younger children.[30] The risk of developing renal stones is 6-10%.[31] The ketogenic diet may cause hypercalciuria, urine acidification and hypocitraturia, all increasing the risk of renal stones. Adequate hydration is necessary for children co-medicated with carbonic anhydrase inhibitors. Urine alkalization should be considered for children with high risk for renal stones including those with high urine calcium to creatinine ratio. Changes in lipid profile include elevated total

cholesterol, triglycerides, low-density lipoprotein and very low-density lipoprotein. The anti-atherogenic apolipoprotein A containing lipoprotein (high-density lipoprotein) is significantly reduced.[32] The MCT diet causes fewer changes on serum lipids.[33] Overall, no long term atherogenic complications have been reported. Mild carnitine depletion may occur early in the ketogenic diet treatment without clinical symptoms.[34] Routine carnitine supplementation is controversial, however, it can be considered in children with unexplained fatigue. Finally, experimental studies showed possible memory impairment while other studies documented improvements on cognition and behavior.[35,36] Increased alertness is often observed, even before discontinuing AEDs. Several other rare side effects were reported including cardiomyopathy, QT prolongation, acute pancreatitis, vitamin D and calcium deficiency, mineral deficiency, platelet dysfunction, neutrophil dysfunction, osteoporosis, hypoproteinemia, renal tubular acidosis, pancreatitis, and basal ganglia changes.

Efficacy. Recent meta-analysis of studies published from 1925 to 1998, including both classic and MCT diet, showed that 37% of patients had >90% seizure reduction, and an additional 30% had 50-90% seizure reduction.[37] The largest prospective study to date was performed by the Pediatric Epilepsy Group at Johns Hopkins Hospital.[38] Overall, 75 of 150 children had >50% reduction in seizure frequency and 30 children had >90% seizure reduction. Only 7 children became completely seizure free.[38] The same cohort was followed for up to 6 years and 20 children were found to be completely seizure free.[39] An additional 21 children had >90% seizure reduction on long-term follow-up.[39] A multicenter prospective study involving 7 comprehensive epilepsy centers included 51 children.[40] The study revealed 55% with >50% seizure reduction at 6 months, and 40% at one year.[40] Additional beneficial effects on cognitive function and neurodevelopment have also been documented.[41,42] Adolescents and adults had a similar response to the diet.[43,44] However, the ketogenic diet has been thought to work best in children for theoretical reasons related to efficacy of ketone extraction by the brain.[45] No differences were found between the efficacy of the MCT diet when compared to the classic ketogenic diet.

Applicability in Saudi Arabia. The ketogenic diet is applied only in one center in the Kingdom of Saudi Arabia, which is the King Faisal Specialist Hospital and Research Centre in Jeddah. Over 2 years (2002-2004), 8 children with intractable epilepsy resistant to multiple AEDs were included. These children were not surgical candidates. We retrospectively reviewed their charts to assess their outcome (**Table 1**). Their ages ranged between 1-14 years (mean 5). The male to female ratio was 3:1. All children had multiple seizure types, daily seizures (averaged 6/day), and were tried on multiple AEDs (mean 5.5). Following the introduction of the ketogenic diet, the number of AEDs was reduced to a mean of 2.5. Three children (38%) showed >50% seizure reduction at 6 months (**Table 2**). As well, the level of alertness improved in 4 (50%) children, 2 of them with no impact on the

Table 1 - Patients managed with ketogenic diet at King Faisal Specialist Hospital & Research Centre, Jeddah, Kingdom of Saudi Arabia.

No.	Age (yrs)	Gender	Epilepsy syndrome	Seizure count at onset	No. of AEDs at onset	No. of AEDs on diet	Route	Imaging
1	8	F	SMEI	12/day	4	3	GT	Brain atrophy
2	2	M	SMEI	7/day	3	3	GT	Brain atrophy
3	4	M	SMEI	12/day	7	2	Oral	Normal
4	14	F	LGS	6/day	7	2	GT	Dysgenesis
5	3.5	M	LGS	7/day	5	3	Oral	Normal
6	1	M	-	3/week	7	3	GT	Dysgenesis
7	4	M	-	4/day	5	3	Oral	Dysgenesis
8	5	M	-	2/day	8	4	GT	Brain atrophy

SMEI = Severe myoclonic epilepsy of infancy, LGS = Lennox Gastaut Syndrome, GT = Gastrostomy tube, AED - antiepileptic drugs

Table 2 - Outcome following the introduction of the ketogenic diet in the 5 children with favorable response.

No.	Seizures	Alertness	Neurodevelopment
1	Reduction > 50%	Improved	Improved
2	Reduction > 50%	Improved	No improvement
3	Reduction > 50%	No improvement	No improvement
4	No response	Improved	No improvement
5	No response	Improved	No improvement

seizures. Neuro-developmental outcome improved in one child who also had improved seizures and alertness (**Table 2**). Our outcome is less favorable when compared to the published literature. Though our total number is small, our lower efficacy figures relate mainly to poor compliance and follow-up. Many families were living outside the Jeddah area and used over the counter medications intermittently, which resulted in interrupted ketosis. Most medication can be obtained over the counter in our country with minimal restrictions. Many of these antibiotics, antipyretics, and antitussive drugs are not sugar free and can result in significant setbacks in the management plan. Some of our children encountered intolerable side effects, which were mainly gastrointestinal complaints, resulting in poor compliance. All families complained about the extra effort needed for diet preparation and the social restrictions characterizing the diet. However, our efficacy outcome is encouraging and a better focused program with more intense parent education and stricter follow up is being developed. We conclude that the ketogenic diet is an important non-pharmacological treatment option for children with refractory epilepsy. Prospective studies and program developments are needed to further assess the long-term efficacy and tolerability in Saudi children.

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