

Letter to the Editor

A newer horizon in non-pharmacological management of intractable epilepsy of childhood: the ketogenic diet

Sir,

The ketogenic diet (KD) is a high fat, low carbohydrate and adequate protein diet that was formulated in the early 1920s as a treatment of intractable epilepsy, when only bromides and phenobarbitones were available. With the discovery of phenytoin in 1935 and other anticonvulsants in subsequent decades its popularity gradually waned off but recently KD has got a resurgence in the management of intractable epilepsy especially of childhood onset, despite the availability of increasing number of new Antiepileptic drugs and surgical techniques.¹

Ketogenic diet is a restrictive diet composed of fat to protein and carbohydrate in ratio of 4:1 by weight with fats accounting for 90% of source of energy. It mimics the biochemical changes of starvation (ketosis) with major shift in cerebral energy metabolism so that ketone bodies become the primary source of energy for the brain. Normally the carbohydrate contained in food gets converted into glucose which acts as a fuel for body and brain function. However, if there is little carbohydrate in diet, the liver preferably convert fat into fatty acids and ketone bodies. These ketone bodies replaces glucose as source of energy in brain, an elevated level of ketone bodies produces a state of ketosis which leads to reduction in frequency of epileptic seizures.² A mixture of long chain triglycerides (LCT) esp.: PUFA are added as a source of fats in a ratio of 4:1 but to increase the palatability sometimes medium chain triglycerides (MCT) as coconut oil are used in 3:1 ratio which produces more ketosis and more efficiently absorbed with lesser gastrointestinal side effects.³ To ensure adequate growth just enough protein i.e., 1 gm/kg is being added in diet however carbohydrates are largely excluded to only 10-15 gm/day so no sugar, grains, bread and starchy fruits.

Indications of ketogenic diet

KD is instituted as adjuvant therapy in children (2-10 years) and adults with medically refractory epilepsy. It is generally effective in all seizure types but particularly in atonic, myoclonic and atypical absence seizures when instituted early in course of disease. Notoriously difficult to control epileptic syndromes like Lennox-Gastaut syndrome, Infantile spasm, tuberous sclerosis may often be benefited from KD.⁴ The diet is treatment of choice or even life-saving in children with glucose transporter GLUT-1 deficiency and in pyruvate dehydrogenase deficiency. In both these conditions, utilization of source

of energy other than glucose for brain metabolism can prevent seizure by providing acetyl CoA directly to TCA cycle without prior glycolysis.⁵ Overall KD is more effective in children than adults because children produce higher degree of ketosis than adults and the brain of children preferably uses ketone bodies as substrate compared to adults.⁶

Mechanism of action of KD

Institution of KD leads to major changes in basic biochemistry and physiology of central nervous system. The following mechanism of action are suggested for efficacy of KD in preventing seizures: 1. Adenosine upregulation by modulation of synaptic plasticity and neuroglial interaction. 2. Inhibition of excitatory glutamatergic transmission by increase in GABA activity. 3. Reduction in carbohydrate glycolysis and kindling associated with seizure inhibition. 4. Activation of ATP dependent potassium pump with resultant reduction of reactive oxygen species and 5. Synaptic inhibition of motor cortical pathways.

Similarly direct negative effect of caloric restriction and excess ketone bodies on seizure activity is also been postulated.^{7,8}

Initiation and monitoring of KD

To get the optimum results, the KD should be instituted early in course of disease with the best results reported in 2-5 years age group. The diet is initiated under close medical supervision of a dedicated team of physician, biochemist, dietician and trained nurse preferably in hospital with a practical strict and rigid protocol. The following steps should be considered:

- Metabolic screening of serum amino acids (AA) and lactate, urinary AA and organic acid along with carnitine profile.
- Attainment of an initial state of ketosis with 24-72 hours fasting.
- Gradual increase of ketogenic ratio in diet from 1:1 to 4:1 within 4-5 days.
- Supplementation of essential vitamins and minerals as KD is not a balanced diet.
- Restrict caloric requirement to 75%.
- The Antiepileptic drug in use to be continued.
- No additional food is permitted (like biscuit, cold drinks and chocolates, not even sugar free) as KD is

not a supplementary diet. A strict watch over carbohydrate consumption is exercised because with carbohydrate intake the stage of ketosis is lost and patient can develop a break through seizure in less than an hour.⁹

The clinical response of KD is generally visible in a week time with attainment of state of significant ketosis but it takes around 3 months for its optimal anticonvulsant effect. Monitoring of urinary ketones periodically (to keep 4+ i.e., 160 mg/dl) suggest the compliance of diet. If ketone levels are less, then 24 hours fast with clear fluid is advised to improve state of ketosis but if signs of symptomatic ketosis appear then small quantity of orange juice is given. The child on KD is advised for regular follow up 3 monthlies during first year of therapy and later every 6 monthly visits. However, infants, those with cerebral palsy, grown retardation and patients with compliance issues and inter current illnesses are advised for early followup.¹⁰

Contraindications of KD

KD is contra indicated in children with following metabolic syndromes: 1. Pyruvate carboxylase deficiency. 2. Mitochondrial disorders. 3. Fatty acid oxidation defects. 4. Acute intermittent porphyria and 5. Carnitine deficiency.

Adverse effects and problems with KD

Being an unpleasant & bland diet with narrow food choice tagged with strict dietary regimen, compliance becomes the major issue with young children on KD. The efficacy of KD is related with its compliance which is the major determinant and challenge with its use. The common adverse effects with diet institution are gastro intestinal like nausea, vomiting, diarrhea or constipation along with development of hypoglycemia. The occurrence of hypoglycemia early in course of dietary institution pose a major problem as it requires intravenous glucose which result in immediate loss of ketosis and break thru seizure. The maintenance phase of KD is complicated by weight loss, hypoproteinemia, hyperlipidemia, slow growth, pancreatitis and renal stones.^{11,12}

KD and antiepileptic drugs

In clinical setting KD is often considered as last resort for medically refractory epilepsy. Most patients beginning with KD already had extensive trials of various combinations of antiepileptic drugs (poly therapy). With use of KD, many patients are able to discontinue or at least reduce their antiepileptics with a corresponding decrease in sedation and other side effects. The available data support that KD is more effective with sodium valproate suggesting a possible synergistic effect.^{13,14}

The goal is to maintain KD for 2 years or until the patient is seizure free off medications for a year. The best clinical advice is to ensure that the KD is working and then slowly wean antiepileptic drugs, one at a time. The diet is weaned off with gradual decrease in ketogenic ratio and introduction of carbohydrates. In case of seizure recurrence, KD can be reinstated with nearly 50% achieving seizure control with drugs and KD.¹⁵

Efficacy of KD

The efficacy of KD is variable with 90% reduction in overall seizure in one third, 50% reduction in half and almost complete seizure control in remaining. It has been recommended that at least 3-month trial of KD is must before assuming it to be ineffective.¹⁶ Children with refractory epilepsy are more likely to be benefited from KD than from trying another antiepileptic. Additionally, improvement in cognition, behaviors, sleep pattern, alertness with reduction of poly antiepileptic dosage add to the indirect beneficial effect of KD in use.¹⁷

Future applications of KD

Although primarily indicated for medically refractory epilepsy of childhood, KD has various effects on bioenergetics in all age group. There is emerging and encouraging reports of its beneficial role in a neurological as well non-neurological conditions of adults like amyotrophic lateral sclerosis (MND), Alzheimer dementia, Parkinson's disease, depression, PCOD and even in diabetes mellitus.

Ketogenic diet a high fat, adequate protein and low carbohydrate restrictive diet has a long history of its use in intractable epilepsy of childhood. The diet produces biochemical changes mimicking that of starvation. The diet is indicated as an adjuvant therapy in children (2-10 years) with intractable epilepsy and is generally effective in all type of seizure semiology especially atypical absence, myoclonic and atonic. The difficult to treat epilepsy syndrome mainly tuberous sclerosis, infantile spasm and Lennox-Gastaut syndrome may respond well to KD if instituted early in course of disease.¹⁸

KD induces its antiepileptic response by changing the basic physio-biochemistry of central nervous system by activation of ATP dependent potassium pump, adenosine upregulation, inhibition of excitatory glutamatergic transmission, synaptic inhibition of cortical motor pathways etc. The low calories intake and excess ketone bodies further accentuate the response of KD.

As KD is not a balanced diet so essential vitamins and minerals are supplemented to maintain adequate growth. The clinical response is generally seen within 5-7 days but it takes around 3 months to produce its optimal anticonvulsant effect. The commonly encountered side effects in initial period includes nausea, vomiting,

constipation, diarrhea and hypoglycemia. The antiepileptic drug in use should be continued with KD with aim to gradually reduce or even withdraw over a period of 2 years or until the patient is seizure free off medications for a year or so. Around 30% children show more than 90% reduction in seizure frequency, 20% show complete seizure control while remaining 50% show substantial decrease in seizure frequency.¹⁹ The unique mode of action of KD expand its horizon as future implication in various diseases like Parkinson's disease, Alzheimer disease, motor neuron disease, diabetes mellitus apart from childhood epilepsy.

KD is an effective therapy for medically refractory epilepsy of childhood. The patient acceptability and palatability pose a reasonable issue for it is compliance. Liquid based ready to mix formulation for infants and externally fed patients proved to be an effective measure in increasing its acceptability. The unique physiologic and metabolic state that dampens aberrant neuronal excitability and results in seizure control makes it worth trying alternative regardless of seizure or epilepsy type.

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Cite this article as: Chaudhary A, Chaudhary B. A newer horizon in non-pharmacological management of intractable epilepsy of childhood: the ketogenic diet. *Int J Contemp Pediatr* 2021;8:958-60.