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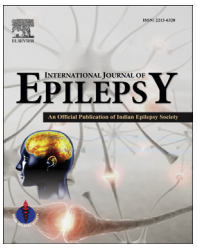

Review Article

# Dietary therapy in childhood epilepsy, an overview

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ABSTRACT

This review highlights the current consensus guidelines regarding use of dietary therapy in childhood epilepsy. Comprehensive search was done in the electronic database, journals, reference lists and dissertations related to the field. In childhood epilepsy, about one-third patients are medically refractory. Surgical resection is an effective modality only in a third of these cases. Dietary therapy causes upto 30–40% reduction in seizure frequency in drug refractory epilepsy. The various forms of dietary therapies described are ketogenic diet, modified Atkins diet and low glycemic index treatment. Apart from ketogenesis, the ketogenic diet also exerts its effect by modulating brain energetics and neurotransmitter circuitry. The classical ketogenic diet comprises of fat to carbohydrate ratio of 4:1 (in terms of weight in grams). Modified Atkins diet is restrictive only for carbohydrates (≤20 g per day). Low glycemic index treatment allows carbohydrate of upto 60 g per day with food items having glycemic index of less than 50. Consensus recommendations for indications and contraindications of dietary therapy in childhood epilepsy have been formulated. Moreover caution has to be warranted for various metabolic and systemic side effects described with this form of therapy. Laboratory and clinical assessment prior to initiation and periodically on therapy is recommended. A trial of dietary therapy is labeled as failure only if there is no response even after 12 weeks of therapy. There is research ongoing globally on dietary therapy with preliminary encouraging reports in status epilepticus and other neurological conditions like migraine, brain tumor and autism.



Around one-third patients with epilepsy have medically intractable epilepsy or suffer from adverse effects of drugs of which only a third have surgically remediable lesions.[1] Medical intractability is defined as failure of 2 or more appropriately chosen antiepileptic drugs (in combination or monotherapy) given in optimal dosage to achieve sustained seizure freedom (atleast 3 times the pre-intervention inter-seizure interval or 1 year, whichever is longer). From patient's point of view, intractability depends on the effect of seizures on daily functioning and adverse effects of drugs whereas from a physician's perspective this would be governed by the accuracy of

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diagnosis, natural history of the epilepsy syndrome and available treatment options.[2,3]

Ketogenic diet is a mode of treatment used particularly in children with intractable epilepsy. Studies across the world have shown upto 30–40% reduction in seizure frequency with dietary therapy.[4]

## 1. Chronology of evolution

Fasting associated seizure control was first documented by Dr. Rawle Geylin in early twentieth century. Wilder discovered a high fat, low carbohydrate diet which could serve the same purpose and christened it ketogenic diet. With the discovery of antiepileptic drugs like phenytoin, valproate and carbamazepine, this was not a very talked about modality of antiepileptic therapy for the major part of 20th century. In 1993, a 20-month-old boy from California named Charlie was treated with ketogenic diet at the John Hopkins Hospital for his medically refractory epilepsy leading to rapid seizure freedom. The very next year saw the creation of the Charlie foundation to promote ketogenic diet related research. Various animal and human studies have been performed since in this field. Different forms of conventional and liberal dietary therapy options have come up. In numerous nonepileptic neurological conditions usefulness of dietary therapy as a treatment option is being evaluated.[5]

## 2. Biological plausibility

Although the exact mechanism of action of ketogenic diet have always eluded researchers, several hypotheses have come up. Various animal and human studies have reinforced the fact that ketone body formation is central to its mechanism of action. Ketogenesis occurs as a result of fatty acid oxidation in the liver. Acetoacetate and β hydroxybutyrate are the primary ketone bodies generated, however there is no mechanism in the liver to convert it back to fatty acids, leading to a state of net ketone bodies' production. Brain readily uses ketone body as fuel with its uptake facilitated by a monocarboxylic transport system. The enzymatic machinery mediating the breakdown of ketone bodies in the brain has maximal expression in childhood accounting for more utilization of ketone bodies. The various proposed mechanisms for its antiseizure action include carbohydrate reduction, activation of energy dependent potassium channels through mitochondrial metabolism, inhibition of mammalian target of rapamycin pathway (Mtor) and excitatory glutamatergic transmission. With carbohydrate reduction there is inhibition of glycolysis and kindling associated epileptogenesis. A very important pathway by which ketogenic diet improves mitochondrial metabolism is reduction in reactive oxygen species. The Mtor pathway is modulated by altered bioenergetics secondary to ketosis which exerts its antiseizure effect by altering dendritic spine structure, effecting neurotransmitter release, ion channel movement and synaptic protein expression. Adenosine, an endogenous anticonvulsant (modulates neuroglial interactions and synaptic plasticity) is also stimulated by ketogenic diet.[6,7]

The anticonvulsant effect of ketogenic diet is delayed by 1–2 weeks after initiation of ketosis. This is because secondary biochemical changes in the brain other than ketonemia also play a significant role in it.

**Table 1 – Various pathways of mechanism of action of ketogenic diet.**

a) Carbohydrate reduction: Glycolysis and kindling associated seizure inhibition
b) Activation of ATP dependent potassium channels by modulating mitochondrial metabolism: Reduction of reactive oxygen species
c) Inhibition of Mtor pathway: Structural, biochemical and molecular changes at the level of synapse
d) Inhibition of excitatory glutamatergic transmission
e) Adenosine upregulation: Modulation of neuroglial interaction and synaptic plasticity

The various putative pathways of anticonvulsant action of ketogenic diet have been tabulated (Table 1).

## 3. Composition

### 3.1. *Classic ketogenic diet*

The classic ketogenic diet, which is usually long chain triglyceride (LCT) based, is calculated in terms of ratio of grams of fat to the grams of protein plus carbohydrate (4:1) with 90% of the energy coming from fat. However the medium chain triglyceride (MCT) based has higher ketogenic potential than LCT, thus decreasing the amount of fat intake, allowing more carbohydrate and protein.[8] Efficacy studies don't show any significant difference between the two diets, however the MCT based diet have better tolerability.[9] Nearly 60% of energy comes from fat in the MCT based diet. There is associated abdominal cramps, diarrhea and vomiting. A mix of LCT and MCT with the latter contributing for 40–50% of the energy, achieves ketosis without any significant gastrointestinal side effects. Usually ratios of 3:1 and 4:1 are used. However a recent study comparing 2.5:1 to 4:1 diet in children upto 5 years of age has shown no significant difference in terms of seizure control with better adverse effect profile in the former.[10] Liquid based ketogenic diet formula mixes are coming up which will increase the applicability of ketogenic diet in infants and enterally fed children.[11,12]

### 3.2. *Modified Atkins diet*

In 1970, Robert C. Atkins developed The Atkins diet for the purpose of weight loss. Although carbohydrate intake is restricted (10–20 g/day), in contrast to the ketogenic diet, it does not restrict protein intake or daily calories. It allows meals containing 65% fat, 25% protein and 10% carbohydrates with a ketogenic ratio of 1:1.[8,13]

### 3.3. *Low glycemic index therapy*

In pursuit of liberalizing ketogenic diet, the fact that children on classical ketogenic diet have stable blood glucose, gave birth to the concept of low glycemic index therapy (LGIT). This form of diet allows daily carbohydrate intake upto 40 to 60 g per day with preference for those minimally affecting blood glucose levels (glycemic index <50).[8]