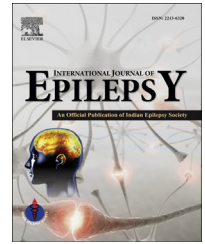


Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://www.journals.elsevier.com/international-journal-of-epilepsy>

Review Article

Dietary therapy in childhood epilepsy, an overview



Sheffali Gulati*, Biswaroop Chakrabarty

Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029, India

ARTICLE INFO

Article history:

Received 7 February 2014

Accepted 21 March 2014

Available online 19 April 2014

Keywords:

Epilepsy

Ketogenic diet

Intractable

Low glycemic index therapy

Modified Atkins diet

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.

Copyright © 2014, Indian Epilepsy Society. Published by Reed Elsevier India Pvt. Ltd. All rights reserved.

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

* Corresponding author. Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029, India. Tel.: +91 9868397532.

E-mail address: sheffaligulati@gmail.com (S. Gulati).
<http://dx.doi.org/10.1016/j.ijep.2014.03.002>

2213-6320/Copyright © 2014, Indian Epilepsy Society. Published by Reed Elsevier India Pvt. Ltd. All rights reserved.

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

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

secondary biochemical changes in the brain other than ketonemia also play a significant role in it.

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

Table 2 – Indications and contraindications for ketogenic diet.**Indications**

1. Syndromic epilepsy
 - a) Myoclonic astatic epilepsy (Doose syndrome)
 - b) Severe myoclonic epilepsy of infancy (Dravet syndrome)
 - c) West syndrome
 - d) Tuberous sclerosis
2. Inborn errors of metabolism
 - a) Pyruvate dehydrogenase deficiency
 - b) GLUT-1 deficiency

Contraindications

1. Disorders of carnitine metabolism and transport
2. Fatty acid oxidation disorders
3. Pyruvate carboxylase deficiency
4. Porphyria

4. Indications and contraindications

In 2009 The International Ketogenic Diet Study Group laid down the recommendations for ketogenic diet in medically intractable epilepsy. However there are some conditions for which early initiation of dietary therapy has been proposed (Table 2).⁸ In GLUT-1 deficiency syndrome and pyruvate dehydrogenase deficiency, it is the treatment of choice. In both these conditions the underlying metabolic defect is bypassed as ketones provides alternative fuel to the brain.^{14,15} In various studies, syndromic epilepsies such as Dravet, Doose and West syndrome, genetic causes like Tuberous sclerosis have all shown good response to ketogenic diet. Preliminary reports have shown beneficial effect even in Lafora body disease, Landau–Kleffner syndrome, Rett syndrome and subacute sclerosing panencephalitis. Anecdotally seizure improvement with ketogenic diet in cases of phosphofructokinase deficiency, glycogenosis type V and respiratory chain defects have also been reported.⁸

The absolute contraindications to the use of ketogenic diet are notably lipid metabolism defect, pyruvate carboxylase deficiency and porphyria (Table 2). In disorders of fatty acid oxidation, ketogenic diet and fasting would precipitate an acute life threatening metabolic crisis. Deficiency of pyruvate decarboxylase which converts pyruvate to oxaloacetate, negatively effects the functioning of Krebs cycle. In porphyria, acute crisis is precipitated as a state of carbohydrate deficiency is created.⁸

Metabolic screening prior to initiation of ketogenic diet is recommended, if the patient has developmental delay, cardiomyopathy, hypotonia, exercise intolerance, myoglobinuria or easy fatigability.⁸ There is no consensus guideline for use of ketogenic diet in focal epilepsies, however decisions may be taken on an individual basis.^{8,16}

5. Adverse effects

In view of the various side effects enumerated below, strict monitoring on part of the neurologist and dietician is warranted in patients on dietary therapy.¹⁷

- a) The various metabolic side effects reported are hypercholesterolemia (upto 59%), hyperuricemia (upto 26%), metabolic acidosis, hypomagnesemia, hypoalbuminemia, aminoacid deficiency, hypocalcemia and carnitine deficiency.^{8,18}
- b) Upto half of the patients on ketogenic diet report gastrointestinal symptoms like vomiting, pain abdomen, diarrhea and constipation.^{8,18}
- c) In upto 7% cases, renal stones have been seen, majority being urate stones.⁸
- d) As far as effect on growth parameters are concerned, more clarity is required through future studies. Although in one retrospective analysis it was seen that 86% of children had slowed linear growth irrespective of age, duration of diet or composition, another prospective study with more than 200 children showed that only younger children had delayed growth whereas older children grew normally.⁸
- e) Cardiomyopathy and prolonged QT interval have been reported. Anecdotal reports of selenium deficiency and pancreatitis are also present.⁸

6. Prescription and maintenance

6.1. Prediet management

Preparing the family and the child for expectations in terms of seizure reduction, need for antiepileptic medications and cognitive improvement is paramount to the overall outcome and success of dietary therapy. Local and traditional custom based factors which may act as potential barriers to administration of diet should also be discussed.

The initial steps include recording the anthropometric parameters and detailed dietary history taking which includes usual preferences, dislikes and allergies. The carbohydrate status of anticonvulsant medications that the child is on should be reviewed and accordingly changes should be made.

There are various laboratory tests recommended prior to initiation of dietary therapy (Table 3). Metabolic screening is recommended if the cause for epilepsy is still unknown or there is progressive encephalopathy. A family history of renal calculi warrants a renal ultrasound.⁸

Table 3 – Prediet laboratory investigations (7–12 are done only when clinically indicated, rest are done in all cases).

1. Hemogram with platelet count
2. Serum sodium, potassium, calcium, phosphate, magnesium, zinc, selenium
3. Renal and liver function tests including total protein and albumin
4. Fasting lipid profile
5. Urine calcium creatinine ratio
6. Arterial blood gas including bicarbonate and lactate levels
7. Electroencephalogram
8. ECG, echocardiogram
9. Renal ultrasound
10. Cerebrospinal fluid analysis
11. Urine gas chromatography mass spectrometry
12. Blood tandem mass spectrometry

6.2. Diet initiation

Conventionally ketogenic diet is initiated using a fasting protocol requiring hospital admission. The duration of fasting may last upto 72 h until significant urinary ketosis is achieved (urine ketones are more than 80 mg/dl), serum β hydroxybutyrate is greater than 1.5 Mm or whole blood glucose is less than 45 mg/dl. However fasting may be associated with hypoglycemia, acidosis, dehydration, nausea, vomiting, anorexia and lethargy. Once ketosis is achieved, calories are increased on a daily basis by one-third keeping the ketogenic ratio constant. In recent times a more liberal approach has found favor, which describes gradually increasing the ketogenic ratio starting from 1:1 and advancing to 4:1 within 4–5 days or earlier if significant urine ketosis is achieved. Usually significant ketosis occurs in either group within a 1 week, with the fasting group demonstrating it a bit earlier whereas the nonfasting group showing lesser adverse effects.¹⁹

However the consensus regarding need for hospitalization is still evolving. The liberal forms of diet, viz., MAD and LGIT, can be routinely advised on an outpatient basis.

Along with dietary therapy, all patients should be started on sugar free multivitamin, trace minerals, calcium and vitamin D supplements.⁸

6.3. In combination with other antiepileptic therapies

With regard to antiepileptic drug therapy, there are certain situations which warrant caution. These include monitoring for secondary carnitine deficiency in patients on valproate and serum bicarbonate levels if the patient is on acetazolamide, sulthiame, topiramate or zonisamide. These patients should also be assessed periodically for renal stones and can be started on empirical oral citrate therapy. Usually antiepileptics can be tapered if seizures are reasonably well controlled on dietary therapy, however, while tapering benzodiazepines and phenobarbitone one has to be cautious for seizure exacerbations.⁸

Synergistic effect of ketogenic diet with vagus nerve stimulation has been reported.²⁰

6.4. Maintaining a child on ketogenic diet

During the first year of therapy, a child on ketogenic diet should be followed up 3 monthly. However, in infants, cerebral palsy patients, those with growth parameters around the 5th centile, patients with compliance issues and intercurrent illnesses, early follow ups are recommended. Subsequently even 6 monthly visits are adequate with interim telephone follow ups. Daily urine ketosis monitoring is advised, however serum β hydroxybutyrate is recommended if urinary ketosis doesn't match with seizure status.

At every visit, patient's anthropometric parameters, dietary compliance and intake of supplements should be checked. There are recommended laboratory tests in follow up too (Table 4).

6.5. Discontinuing ketogenic diet

A trial of dietary therapy is labeled as failure only after a period of 12 weeks.²¹ Those with >50% seizure control are

Table 4 – Follow up Laboratory Investigations (7–12 are done only when clinically indicated, rest are done in all cases).

continued for atleast 2 years on dietary therapy, however patients with >90% seizure control with no significant adverse effects can continue it for even longer. Certain conditions like GLUT-1 deficiency and pyruvate dehydrogenase deficiency need lifelong therapy. Nearly 80% patients remain seizure-free amongst those who achieve complete seizure freedom, with high recurrence risk observed in patients with electroencephalographic abnormalities and lesional epilepsy.²²

Under normal circumstances, ketogenic diet is weaned off with gradual decrease in ketogenic ratio and introduction of carbohydrates. Foods with high glycemic indices are introduced only after urinary ketosis stops. In case of seizure recurrence, dietary therapy can be reintroduced with nearly 50% achieving seizure control with drugs and/or ketogenic diet.^{22,23}

7. Efficacy of various forms of ketogenic diet

7.1. Classic ketogenic diet

Most of the studies till date have reported that in early childhood epilepsy, after 3 months of adequate diet therapy, around 50% and 70% patients have >90% and >50% reduction in seizure frequency respectively whereas in late childhood and adolescence the figures are to the tune of 30% and 50% respectively (Table 5). This is because the machinery utilizing ketone bodies in the brain are more active in the early years and there are more chances of noncompliance with increasing age. Overall around half of the patients are able to continue the diet beyond 1 year. Adding ketogenic diet to standard antiepileptic therapy results in better seizure control.^{10,11,18,24–32}

7.2. Modified Atkins diet

Various prospective as well as randomized trials evaluating the efficacy of modified Atkins' diet in medically refractory epilepsy have been reported (Table 6). Upto 65% and 35% patients respectively have greater than 50% and 90% reduction in seizure at 6 months after initiation of dietary therapy with 80% accepting the diet well beyond 6 months. The only notable side effect reported is constipation. In view of better

Table 5 – Efficacy studies of classic ketogenic diet.

| Author and year | Study population | Intervention | Type of the study | Efficacy and tolerability |
|-----------------------------------|--|---|-------------------------|---|
| Vining et al, 1998 ²⁵ | 51 children, aged 1–8 years, with more than 10 seizures (medically refractory) per week, whose EEG showed generalized or multifocal epilepsy | Classic (4:1) Ketogenic diet | Prospective | At 3, 6 and 12 months frequency of seizures was decreased to greater than 50% in 54%, 55% and 40% respectively. 10% were free of seizures at 1 year 47% remained on the diet at 12 months |
| Freeman et al, 1998 ²⁶ | 150 children, aged 1–16 years, with more than 1 seizure (medically refractory) per week | Classic (4:1) Ketogenic diet | Prospective | At 3, 6 and 12 months frequency of seizures was decreased to greater than 90% in 34%, 32% and 27% respectively 47% remained on the diet at 12 months |
| Kossoff et al, 2002 ⁴⁵ | 23 children with infantile spasm, 5 months to 2 years age | Classic (4:1) Ketogenic Diet | Prospective | At 3, 6, 9, and 12 months - 38%, 39%, 53%, and 46% respectively showed >90% improvement (3 were seizure-free at 12 months) - 67%, 72%, 93%, and 100% respectively showed >50% improvement 56% remained on the diet at 12 months |
| Coppola et al, 2002 ²⁷ | 56 patients with cryptogenic or symptomatic, generalized or partial medically refractory epilepsy, 1–23 years age | Classic (4:1) Ketogenic diet | Prospective | At 3, 6 and 12 months - 37.5%, 26.8%, 17.9% respectively showed >50% improvement |
| Mackay et al, 2005 ²⁸ | 26 patients with medically refractory epilepsy, mean age of 6.1 years | Classic (4:1) Ketogenic diet | Prospective | At 9 months, 16% became seizure-free, 20% had 50–99% reduction in seizures, 28% had <50% reduction in seizures and 36% had no improvement 48% remained on the diet at 12 months |
| Kang et al, 2005 ²⁹ | 199 infants, children and adolescents with medically refractory epilepsy | Classic (4:1) Ketogenic diet | Prospective | At 6 and 12 months, 33% and 25% respectively became seizure-free, 58% and 41% respectively had >50% reduction in seizures 46% remained on the diet at 12 months |
| Hosain et al, 2005 ¹² | 12 children, aged 7 months to 6.5 years with medically refractory epilepsy | Classic (4:1) Ketogenic diet via gastrostomy tube | Prospective | Median seizure reduction at 1 year and 18 months was 61% and 66% respectively Individually, six patients had 90% seizure reduction, one had 75% reduction, three had 50% reduction and two patients did not improve Compliance with diet was 100% |
| Sharma et al, 2009 ¹⁸ | 27 children, aged 6 months to 5 years, with medically refractory epilepsy (at least 1/day or 7/week) | Classic (4:1) ketogenic diet | Prospective | At 6 and 12 months, 15% and 18.5% respectively became seizure-free, 48% and 37% respectively had >50% reduction in seizures 37% remained on the diet at 12 months |
| Mosek et al, 2009 ³¹ | 9 adults, aged 18–45 years, with at least 2 focal seizures/month | Classic (4:1) ketogenic diet | Prospective pilot study | Only 2 patients completed the 12 week period of the study and had >50% seizure control |

(continued on next page)

Table 5 – (continued)

| Author and year | Study population | Intervention | Type of the study | Efficacy and tolerability |
|--------------------------------|--|---|--|--|
| Seo et al, 2007 ³⁰ | 76 patients with refractory childhood epilepsy | Classic (4:1) versus 3:1 ketogenic diet | Randomized clinical trial | Over 3 months, 55% on the 4:1 diet and 30.5% on the 3:1 diet became seizure-free ($p < 0.05$) Gastrointestinal symptoms were observed in 13.9% patients with the 3:1 diet and 35% patients with the 4:1 diet ($p < 0.05$) |
| Neal et al, 2008 ²⁴ | 145 children, aged 2–16 years, with medically refractory epilepsy (at least 1/day or 7/week) | Classic (4:1) ketogenic diet | Randomized controlled trial (control arm: standard treatment using antiepileptics) | After 3 months, the mean percentage of baseline seizures was significantly lower in the diet group than in the controls (62.0% vs 136.9%, $p < 0.0001$) 28 children (38%) in the diet group had greater than 50% seizure reduction compared with four (6%) controls ($p < 0.0001$) Five children (7%) in the diet group had greater than 90% seizure reduction compared with no controls ($p = 0.0582$). |
| Neal et al, 2009 ³² | 145 children with medically intractable epilepsy | Classic (4:1) versus MCT based ketogenic diet | Randomized clinical trial | After 3, 6, and 12 months there were no statistically significant differences in mean percentage of baseline seizures between the two groups (3 months: classical 66.5%, MCT 68.9%; 6 months: classical 48.5%, MCT 67.6%; 12 months: classical 40.8%, MCT 53.2%; all $p > 0.05$) There were no significant differences between groups in numbers achieving greater than 50% or 90% seizure reduction No significant differences in tolerability |
| Raju et al, 2011 ¹⁰ | 38 children, aged 6 months to 5 years, with medically intractable epilepsy | Classic (4:1) versus 2.5:1 ketogenic diet | Randomized clinical trial | At three months, 58% in the 4:1 group and 63% in the 2.5:1 group had more than 50% reduction in seizures ($p = 0.78$), 26% in the 4:1 group and 21% in 2.5:1 group became seizure-free |

tolerability and acceptability, it seems to be a suitable option for refractory adolescent and adult onset epilepsies.^{13,33–39}

7.3. Low glycemic index therapy

Initial efficacy data from pilot studies are encouraging (Table 7). Studies have shown that upto 50% patients have greater than 90% reduction in seizures and 70–80% are compliant on the diet for upto 6 months.^{21,40} In a recently completed unpublished study in India in 40 children with refractory epilepsy, upto one-third showed around 50% seizure control with nearly 90% tolerating the diet at the end of 3 months.

7.4. Ketogenic diet in status epilepticus

Ketogenic diet is evolving as a treatment option in super refractory status epilepticus. Super refractory status epilepticus is defined as recurrent or persisting status beyond 24 h on

appropriate antiepileptic and anesthetic therapy. Currently ketogenic diet is considered in super refractory status epilepticus not responding to surgery and immunotherapy. There are case reports of positive response in children with fever induced refractory epileptic encephalopathy and adults with refractory status epilepticus. In two children with non-convulsive status beneficial effect of modified Atkin's diet has been described. Recently an adult patient with super refractory status epilepticus was successfully initiated and maintained on parenteral ketogenic diet with subsequent shift to enteral preparation.^{41,42}

8. Cognitive and behavioral benefits of ketogenic diet

Prospective studies evaluating the effect of ketogenic diet on cognition are lacking. However anecdotal and parental

Table 6 – Efficacy studies of Modified Atkins Diet.

| Author and year | Study population | Intervention | Type of the study | Efficacy and tolerability |
|-----------------------------------|--|---------------------------------------|---|---|
| Kossoff et al, 2006 ¹³ | 20 children aged 3–18 years with medically refractory epilepsy (>2/week) | Modified Atkins diet | Prospective | At 6 months, 65% and 35% respectively had >50% and >90% reduction in seizures 80% tolerated diet at 6 months |
| Kang et al, 2007 ³⁶ | 14 children with intractable childhood epilepsy | Modified Atkins diet | Prospective | At 6 months, 36% and 21% respectively had >50% and 100% reduction in seizures 86% tolerated diet at 6 months |
| Kossoff et al, 2008 ³⁷ | 30 adults aged 18–53 years with medically refractory epilepsy (atleast 1/week) | Modified Atkins Diet (15 g/day) | Prospective | 47% had a >50% seizure reduction after 1 and 3 months on the diet, 33% after 6 months 70% continued the diet beyond 3 months |
| Weber et al, 2009 ³⁸ | 15 children with medically refractory epilepsy (atleast 1/week) | Modified Atkins diet | Prospective | 40% had a seizure reduction of more than 50% at 3 months 20% continued the diet at 12 months |
| Miranda et al, 2011 ³⁹ | 33 children with medically refractory epilepsy | Modified Atkins diet | Prospective | After 3 months, 52% and 42% respectively had >50% and >90% seizure reduction After 6 months, 39% had >50% seizure control At 12 months, 27% and 12% had respectively >50% and >90% seizure reduction 52% remained on the MAD for atleast 12 months |
| Sharma et al, 2012 ³⁴ | 15 children, aged 6 months to 3 years with infantile spasm | Modified Atkins diet | Prospective | After 3 months, 40% were spasm free |
| Kossoff et al, 2007 ³⁵ | 20 children with intractable childhood epilepsy | Modified Atkins Diet (10 or 20 g/day) | Randomized Controlled Trial crossover (10 g versus 20 g for initial 3 months and then crossover to the other group) | A significantly higher likelihood of >50% seizure reduction was noted for children started on 10 g of carbohydrate per day at 3 months: 60% versus 10% ($p = 0.03$) Improved tolerability with 20 g per day |
| Sharma et al, 2013 ³³ | 102 children, aged 2–14 years, with medically refractory epilepsy (daily seizures) | Modified Atkins Diet | Randomized controlled trial (control arm being standard antiepileptic treatment) | The mean seizure frequency at 3 months, expressed as a percentage of the baseline, was significantly less in the diet group: 59 ± 54 (95% confidence interval 44–74.5) versus 95.5 ± 48 (95% CI 82–109), $p = 0.003$ The proportion of children with >90% seizure reduction (30% vs. 7.7%, $p = 0.005$) and >50% seizure reduction was significantly higher in the diet group (52% vs. 11.5%, $p < 0.001$) |

Table 7 – Efficacy studies of LGIT.

| Author and year | Study population | Intervention | Type of the study | Efficacy and tolerability |
|---|--|--------------|--|---|
| Coppola et al, 2011 ⁴⁰ | 15 patients, aged 11–22 years with medically refractory epilepsy | LGIT | Retrospective chart review | At 12 months, 40% had a 75–90% seizure reduction, while seizures decreased by 50% in 13.3% and were unchanged in 7 (46.7%) 30% discontinued the diet beyond 5 months |
| Pfeifer et al, 2005 ²¹ | 20 patients with medically refractory epilepsy | LGIT | Prospective | 50% patients had >90% reduction in seizure |
| Lakshminarayan et al (personal communication), 2012 | 40 patients, 2–8 years age with medically refractory epilepsy | LGIT | Randomized controlled trial (control arm was patients on standard antiepileptic therapy) | At 3 months, 33% (1 seizure-free) had >50% seizure reduction as compared to none in the control arm ($p = 0.02$) 88.5% continued the diet at 3 months |

reports show improvement in overall cognition, behavior and alertness, better sleep patterns and improved quality of life.⁴³

9. Ketogenic diet in conditions other than epilepsy

The ketogenic diet has various effects on the bioenergetics. The main underlying phenomena are ketone body production and decrease in blood glucose levels. Ketone bodies raise ATP levels and reduce production of reactive oxygen species through enhanced NADH oxidation and inhibition of mitochondrial permeability transition which in turn stimulates mitochondrial biogenesis and stabilizes synaptic function. Additionally calorie restriction decreases the expression of Brain derived Neurotrophic factor and its receptor tyrosine kinase β , is antiapoptotic and exhibits antiinflammatory action. Researchers are now evaluating its potential role in treatment of other neurological disorders with encouraging reports in autism, migraine, head trauma, stroke, brain tumor, amyotrophic lateral sclerosis and Alzheimer's disease.^{7,44}

10. Conclusion

Ketogenic diet is an effective therapy in medically intractable epilepsy. However close monitoring is required for side effects. Palatability and patient acceptability are still a reasonable issue. Liberal modifications like modified Atkins diet and low glycemic index treatment have been developed which are more acceptable and associated with lesser side effects. Liquid based ready to mix formula preparations for infants and enterally fed patients are a welcome effort in increasing its applicability. Future studies should be planned to evaluate the long term effect of the diet in terms of cognition, behavior, growth parameters and adverse effects like development of metabolic syndrome. Head on randomized trials should be planned comparing the classical ketogenic diet with MAD and LGIT.

Conflicts of interest

All authors have none to declare.

REFERENCES

- Berg AT. Defining intractable epilepsy. *Adv Neurol*. 2006;97:5–10.
- Schuele SU, Lüders HO. Intractable epilepsy: management and therapeutic alternatives. *Lancet Neurol*. 2008;7:514–524.
- Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the adhoc task force of the ILAE commission on therapeutic strategies. *Epilepsia*. 2010;51:1069–1077.
- Levy RG, Cooper PN, Giri P, Pulman J. Ketogenic diet and other dietary treatments for epilepsy. *Cochrane Database Syst Rev*. 2012;3:CD001903.
- Kossoff EH, Zupec-Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. *J Child Neurol*. 2009;24:979–988.
- Danial NN, Hartman AL, Stafstrom CE, Thio LL. How does the ketogenic diet work? Four potential mechanisms. *J Child Neurol*. 2013;28:1027–1033.
- Stafstrom CE, Rho JM. The ketogenic diet as a treatment paradigm for diverse neurological disorders. *Front Pharmacol*. 2012;3:1–8.
- Kossoff EH, Zupec-Kania BA, Amark ZE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia*. 2009;50:304–317.
- Neal EG, Chaffe HM, Edwards N, Lawson MS, Schwartz RH, Cross JH. Growth of children on classical and medium chain triglyceride ketogenic diets. *Pediatrics*. 2008;122:334–340.
- Raju KNV, Gulati S, Kabra M, et al. Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study. *Epilepsy Res*. 2011;96:96–100.
- Kossoff EH, McGrogan JR, Freeman JM. Benefits of an all-liquid ketogenic diet. *Epilepsia*. 2004;45:1163.
- Hosain SA, La Vega-Talbot M, Solomon GE. Ketogenic diet in pediatric epilepsy patients with gastrostomy feeding. *Pediatr Neurol*. 2005;32:81–83.
- Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia*. 2006;47:421–424.
- Klepper J, Leiendecker B. GLUT1 deficiency syndrome. *Dev Med Child Neurol*. 2007;49:707–716.
- Wexler ID, Hemalatha SG, McConnell J, et al. Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets. Studies in patients with identical mutations. *Neurology*. 1997;49:1655–1661.
- Stainman RS, Turner Z, Rubenstein JE, Kossoff EH. Decreased relative efficacy of the ketogenic diet for children with surgically approachable epilepsy. *Seizure*. 2007;16:615–619.
- Wheless JW. The ketogenic diet: an effective medical therapy with side effects. *J Child Neurol*. 2001;16:633–635.
- Sharma S, Gulati S, Kalra V, Agarwala A, Kabra M. Seizure control and biochemical profile on the ketogenic diet in young children with refractory epilepsy—Indian experience. *Seizure*. 2009;18:446–449.
- Bergqvist AG, Schall JI, Gallagher PR, Cnaan A, Stallings VA. Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. *Epilepsia*. 2005;46:1810–1819.
- Kossoff EH, Pyzik PL, Rubenstein JE, et al. Combined ketogenic diet and vagus nerve stimulation: rational polytherapy? *Epilepsia*. 2007;48:77–81.
- Pfeifer HH, Thiele EA. Low-glycemic-index treatment: a liberalized ketogenic diet for treatment of intractable epilepsy. *Neurology*. 2005;65:1810–1812.
- Freeman JM, Kossoff EH, Freeman JB, Kelly MT. *The Ketogenic Diet: A Treatment for Epilepsy in Children and Others*. 4th ed. New York: Demos; 2006.
- Martinez CC, Pyzik PL, Kossoff EH. Discontinuing the ketogenic diet in seizure-free children: recurrence and risk factors. *Epilepsia*. 2007;48:187–190.
- Neal EG, Chaffe HM, Schwartz RH, et al. The ketogenic diet in the treatment of epilepsy in children: a randomised, controlled trial. *Lancet Neurol*. 2008;7:500–506.
- Vining EPG, Camfield PR, Trevathan E. A multicenter study of the efficacy of the ketogenic diet. *Arch Neurol*. 1998;55:1433–1437.
- Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. The efficacy of the ketogenic diet-1998: a prospective

- evaluation of intervention in 150 children. *Pediatrics*. 1998;102:1358–1363.
27. Coppola G, Veggiotti P, Cusmai R, et al. The ketogenic diet in children, adolescents and young adults with refractory epilepsy: an Italian multicentric experience. *Epilepsy Res*. 2002;48:221–227.
 28. Mackay MT, Bicknell-Royle J, Nation J, Humphrey M, Harvey AS. The ketogenic diet in refractory childhood epilepsy. *J Paediatr Child Health*. 2005;41:353–357.
 29. Kang HC, Kim YJ, Kim DW, Kim HD. Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. *Epilepsia*. 2005;46:272–279.
 30. Seo JH, Lee YM, Lee JS, Kang HC, Kim HD. Efficacy and tolerability of the ketogenic diet according to lipid: nonlipid ratios—comparison of 3:1 with 4:1 diet. *Epilepsia*. 2007;48:801–805.
 31. Mosek A, Natour H, Neufeld MY, Shiff Y, Vaisman N. Ketogenic diet treatment in adults with refractory epilepsy: a prospective pilot study. *Seizure*. 2009;18:30–33.
 32. Neal EG, Chaffe H, Schwartz RH, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia*. 2009;50:1109–1117.
 33. 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;54:1–6.
 34. Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet in infantile spasms refractory to first-line treatment. *Seizure*. 2012;21:45–48.
 35. Kossoff EH, Turner Z, Bluml RM, Pyzik PL, Vining EP. A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet. *Epilepsy Behav*. 2007;10:432–436.
 36. Kang HC, Lee HS, You SJ, Kang DC, Ko TS, Kim HD. Use of a modified Atkins diet in intractable childhood epilepsy. *Epilepsia*. 2007;48:182–186.
 37. Kossoff EH, Rowley H, Sinha SR, Vining EPG. A prospective study of the modified Atkins diet for intractable epilepsy in adults. *Epilepsia*. 2008;49:316–319.
 38. Weber S, Molgaard C, Taudof K, Uldall P. Modified Atkins diet to children and adolescents with medical intractable epilepsy. *Seizure*. 2009;18:237–240.
 39. Miranda MJ, Mortensen M, Povlsen JH, Nielsen H, Beniczky S. Danish study of a modified Atkins diet for medically intractable epilepsy in children: can we achieve the same results as with classical ketogenic diet? *Seizure*. 2011;20:151–155.
 40. Coppola G, D'Aniello A, Messana T, et al. Low glycemic index diet in children and young adults with refractory epilepsy: first Italian experience. *Seizure*. 2011;20:526–528.
 41. Shorvon Simon, Ferlisi Monica. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain*. 2011;134:2802–2818.
 42. Strzelczyk A, Reif PS, Bauer S, et al. Intravenous initiation and maintenance of ketogenic diet: proof of concept in super-refractory status epilepticus. *Seizure*. 2013;22:581–583.
 43. Hallbook T, Ji S, Maudsley S, Martin B. The effects of ketogenic diet on behavior and cognition. *Epilepsy Res*. 2012;100:304–309.
 44. Maalouf M, Rho JM, Mattson MP. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. *Brain Res Rev*. 2009;59:293–315.
 45. Kossoff EH, Pyzik PL, McGrogan JR, Vining EPG, Freeman JM. Efficacy of the ketogenic diet for infantile spasms. *Pediatrics*. 2002;109:780–783.