THE KETOGENIC DIET

Nutritional Management of Epilepsy

The information explosion in the science of nutrition very often creates the impression that available information is contradictory. Consequently, it is no longer easy to distinguish between fact, misinformation and fiction. The Nutrition Information Centre of the University of Stellenbosch (NICUS) was established to act as a reliable and independent source of nutrition information.

> *"One who is confronted with the task of controlling seizures in a person with epilepsy grasps at any straw. When, some six*
> *Or eight years ago, an osteopathic practitioner in Michigan stated that fasting would cure epilepsy, this seemed like a very*
> *frail straw. . .[but] in many patients there was freedom from seizures during fast."*
> —Lennox, 1928

The Ketogenic Diet (KD) has been in use as a treatment for epilepsy since 1921. It is recommended for children with refractory epilepsy who are not candidates for epilepsy surgery. In addition, the diet has become the first line treatment of GLUT-1 deficiency, pyruvate-dehydrogenase complex efficiency and phosphofructokinase deficiency. Besides its anticonvulsant properties, a growing number of studies has recently demonstrated neuro-protective effects of the KD in various neuro-degenerative disorders (including Alzheimer's and Parkinson's disease, mitochondrial disorders, Rett syndrome) brain tumours, traumatic brain injury and stroke.

WHAT IS THE KETOGENIC DIET?

The ketogenic diet is a valuable therapeutic approach for epilepsy. The diet is high in fat, low in carbohydrate (CHO) and moderate in protein that induces and maintains ketosis by burning fat instead of carbohydrate for energy. It is rigid and strictly monitored. The KD is followed for a period of time in order to control seizures / epilepsy that have, in the past, been unsuccessfully controlled by medication alone or in patients with unacceptable toxicity secondary to their anticonvulsant therapy.

There are 4 versions of diet therapy for epilepsy:

1) The classic KD
2) The MCT (Medium Chain Triglyceride) Diet
3) The Modified Atkins Diet (MAD)
4) Low glycaemic index treatment (LGIT)

The classic KD is a diet in which the ratio of fat to CHO plus protein is 4:1 or 3:1. The patient's ideal body weight (IBW) is used for energy calculations if the patient is of normal weight or obese. Underweight patient's present weight should be used. Patients who are overweight are encouraged to loose the excess weight, but the ketosis does suppress the appetite, which may assist weight loss. When calculating energy requirements, approximately 75%-100% of the recommended daily allowance (RDA) plus basic adjustments for age, build, and IBW as well as activity level are Fluid intake is not restricted. Children may experience thirst and adequate water is recommended to prevent kidney stones. Care should be taken not to offer sugar containing drinks or fruit juices.

The KD was modified to include **MCT** oil due to the high animal fat content of the classic KD, which was unacceptable to some patients. MCT oils are odourless, colourless and tasteless. The MCT oils produce rapid hyperketonemia and may increase hepatic fatty acid synthesis and reduce ketone clearance. The **MCT Diet** allows the patient to eat 100% of the RDA and a wider variety of food(s) together with a less strict CHO while producing the same level of ketosis. However, a high intake of MCT oils can cause gastric discomfort like nausea, vomiting, abdominal cramping and diarrhea. The MCT oils may be given as a mixture of the oils and skimmed milk, which must be sipped slowly to help prevent the unpleasant gastrointestinal symptoms and generally provide 30% to 60% of dietary energy.

The MAD initially restricts carbohydrates to 10 g per day (10 g per day for children, 20 g per day for adults indefinitely), but otherwise protein intake is free and high intake of fat and oils encouraged.

The LGIT is like the MAD initiated at home. Dietetic guidance is needed to ensure energy requirements are met and advice is given on the type and amount of carbohydrate (40—60 g low GI CHO), protein (approximately 20%) and fat (high, approximately 50—60%) used in the daily menu plan. It is slightly higher in carbohydrates (limited to low glyceamic index carbohydrates).

MECHANISM OF ACTION

The exact mechanism is still under dispute and generally unknown. The beneficial effects of the KD are thought to be due to the induced ketosis, acidosis, dehydration and electrolyte changes that occur. Experimental evidence exits for four distinct mechanisms that may contribute to the anti-seizure and other beneficial effects of these diets. These mechanisms include carbohydrate reduction, activation of adenosine triphosphate (ATP)-sensitive potassium channels by mitochondrial metabolism, inhibition of the mammalian target of rapamycin pathway, and inhibition of glutamatergic excitatory synaptic transmission. These mechanisms depend on ketones binding directly to proteins involved in synaptic transmission and changes in metabolic and cell signaling pathways.

WHO SHOULD FOLLOW THE CLASSIC KD DIET?

An international consensus statement notes that if outpatient initiation is considered, several conditions must be met including pre-screening for metabolic disorders, ensuring that the child is in a location close to medical care, and that the KD team must be prepared to provide caregiver education on an outpatient basis.

The diet is quite difficult to institute and to maintain and it should be done under the supervision of a dietitian. In determining the type of patients who should follow this diet, the following factors should be taken into consideration:

1) Type of patient

Ketogenic diet therapy should be considered as a treatment option in pediatric and adult patients with refractory status epilepticus. Classic and MCT KDs can effectively treat epilepsy from infancy through to adulthood. It is more difficult, however, to induce and maintain ketosis in patients younger than 1 year since such patients are more likely to become hypoglycemic. All children with an enteral feeding tube should be initiated on the KD, as there are formulas, which are appropriate for this. Families needing structure and planned meals should be offered the KD.

2) Deficiencies in the GLUT-1 Glucose Transporter and Pyruvate Dehydrogenase (E1) Deficiency

The ketogenic diet is indicated specifically for patients with deficiencies in the GLUT-1 glucose transporter where glucose cannot be transported into the cerebrospinal fluid for use by the brain, and pyruvate dehydrogenase (E1) deficiency where ketone bodies can bypass the enzymatic defect.

3) Seizure type

Regardless of seizure type, if the patient's seizure frequency or severity decreases when he / she is unable to eat, for whatever reason, this may suggest that the KD may play a role in the successfully treatment of his / her epilepsy.

4) Motivation to comply with the diet

This is an important factor, as the diet must be strictly adhered to as minor infringements may precipitate seizures and cause the treatment to fail. The patient, care-giver and family must be informed that this diet needs to be followed for a period of up to 2-3 years and that the diet itself is expensive, time consuming and disruptive to the family life as a whole.

DIET INITIATION, MONITORING AND TITRATION OF THE DIET

Careful monitoring of these patients is important as small amounts of chewing gum, medication (solid dosages are preferred above the fluid formulations), health and beauty products like swallowing toothpaste or mouthwash can inhibit ketosis and cause the diet to fail.

Therapeutic failures can be caused by the presence of illness, non-compliance to the diet, the incorrect calculations or preparation of the diet itself, the diurnal pattern in ketone concentration or the type of diet being used. Ketosis can be re-established by making the patient fast for a brief period of time (i.e. skip a few meals).

The diet can be sustained for years, although most studies show that the diet is generally maintained for 2 years and then slowly withdrawn over a 6 to 9 month period. Sometimes 10 to 32 months are needed before the patient returns to a totally unrestricted diet. If a patient's seizures return or worsen during this withdrawal period, the KD diet should be re-implemented.

Nutrient supplementation

Children receiving the KD (classic or MCT) without nutrition supplementation are at risk of nutritional deficiency due to inadequate intake of nutrients because of the restrictive nature of the KD. These vitamin and minerals include vitamins A, B1,B2, B3, B6, B12, C, D, and K, folate, calcium, phosphate, magnesium, iron, zinc and selenium. A complete nutrition assessment, which includes client food and nutrition history, nutrition-focused physical findings, and laboratory biochemical indices, is recommended to identify potential deficiencies prior to and every one to six months while children are on the KD.

Carnitine should be supplemented if carnitine levels are low or children become symptomatic during the KD treatment.

It is also important to take drug nutrient interactions of the anti-convulsants into consideration.

It is recommended that children following a KD take a daily carbohydrate-free or minimal carbohydrate-containing multivitamin and mineral supplement. As each child's vitamin and mineral requirements vary based on age and gender, vitamin and mineral dosages should be calculated according to Dietary Reference Values while on the KD.

EFFICACY

Data from a systematic review and a Cochrane review, which included four randomized controlled trials, indicates that classic and MCT KDs are efficacious in the treatment of intractable epilepsy in children and adolescents. At least 38% of children treated with KD experienced greater than 50% reduction in seizures at three months. One of the four RCTs showed that classic and MCT KDs are equally effective in decreasing the mean percentage of baseline seizures compared to a control group (no dietary intervention).

Many of the patients who are maintained seizure-free on this diet are able to have their anti-epileptic drugs decreased or withdrawn. This allows many of these children to become more alert and exhibit better behavior. Carefully controlled clinical trails are needed to better assess the efficacy of the diet during its use and after its discontinuation.

Possible Complications

Short term complications

These include dehydration, hypoglycaemia, vomiting, diarrhoea and the refusal to eat. These complications (Table 1) are normally experienced upon initiation of the diet and can be reduced by the gradual implementation of the diet or use of the modified MCT KD.

Long term complications

These complications can occur between 1 week and 2 years on the KD. They include kidney stones (3 – 5%), recurrent infections (2%), metabolic derangements such as hyperuricemia (2%), hypocalcemia (2%), decreased amino acid levels and acidosis (2%), hypercholesterolemia (29 – 59%), irritability, lethargy and the refusal to eat (3 – 9%).

Very long term complications

Kidney stones occur in approximately 1 in 20 children on the ketogenic diet. Oral potassium citrate would appear to be beneficial in the prevention of stone formation but prospective studies using this medication are needed. One study was performed on 195 children started on the ketogenic diet for intractable epilepsy from 2000 to 2005. Children who developed kidney stones were compared with those without kidney stones. Thirteen children in this study population (6.7%) developed kidney stones. The use of oral potassium citrate significantly decreased the prevalence of stones. The prevalence of kidney stones did not correlate with age or the use of carbonic anhydrate inhibitors. The presence of hypercalciuria appeared to be a risk factor for kidney stone formation. Kidney stones were successfully treated by increasing water and fluid intake, alkalinization of the urine and discontinuation of carbonic anhydrase inhibitors, when it was indicated.

Adequate growth and growth monitoring remains a very important role of the dietitian and the medical team. Further research is needed and will help to improve the dietary planning and implementation of the diet.

Table 1: Summary of possible* anticipated side effects of the ketogenic diet:

Metabolic Acidosis Weight loss Inadequate growth *Rapid ketosis/acidosis* Hyperlipidemia *Vitamin, trace element deficiency* Hypoglycemia Hyperuricemia	**Gastro Intestinal** Nausea/emesis (initiation) Constipation (classic KD) Diarrhoea (MCT-KD) Worsening GERD Acute pancreatitis *Hypoproteinemia*
Hematological Low Na, Mg *Anaemia* Easy bruising *Leukopenia*	**Neurological** *Basal ganglia changes* *Coma, Obtundation* *Optic neuropathy (thiamine deficiency)*
Cardiac Prolonged QT syndrome *Cardiomyopathy*	**Infectious disease** *Susceptibility to infection* **Orthopedic** *Fractures*
Renal	**Unknowns**

Symptomatic nephrolithiasis (6%) *Fanconi renal tubular acidosis* Dehydration	Bone Muscle Liver

Italics indicate case reports documented in the literature.

*It is possible effects and patients might not have all at once or only some,

Source: Hartman AL, Vining EPG. Epilepsia, Vol. 48, No. 1, 2007

KD: Ketogenic Diet; MCT: Medium-chain triglyceride; MCT-KD: Medium-chain triglyceride ketogenic diet; GERD: Gastroesophageal reflux disease; Na: Sodium; Mg: Magnesium; QT: Cardiac Output

WHO SHOULD FOLLOW AN ALTERNATIVE OPTION OF THE KD DIET?

The MCT diet is a ketogenic diet that is equal in efficacy. The clinical evidence for the efficacy of the alternative ketogenic diets is limited; however, there are some clinical studies of the MAD and the LGIT to the classical diet and may be considered in some patients.

Current available research supports the efficacy of the modified Atkins diet. With 10 years of use, there are 423 children and adults reported in 31 studies from multiple centers who have under gone MAD. When added together, 187 (47%) patients overall have had a 50% seizure reduction, which is comparable to the results found for the ketogenic diet.

Children from 2 to 6 years/school age, should probably be offered a more liberalized diet, having in mind the benefit of the ‘‘strict’’ start with high fat and lower carbohydrate (10 g per day in the MAD) in the first 1—3 month. Liberalising further can be done after the first 3 months without losing efficacy. In children between 2 and 6 years of age, careful individual evaluation, regarding especially family circumstances and epilepsy type and severity, should be performed, in order to make the best choice for each particular child. Teenagers and adults should primarily be treated with MAD or LGIT, which can be individually tailored to the needs of each patient.

Switching from MAD/LGIT to classical KD should be considered if the liberal diets have shown seizure reduction, which is considered insufficient.

Table 2: Factors to Consider When Selecting a Diet Therapy.

Type of diet	Brief description	Suitability
Clasical Ketogenic Diet	Strictly prescribed recipes for meals and snacks. Very high fat	Young children and those with poor appetites who need small meals and snacks.

Classical 4:1 ratio: 90% fat, 6% protein, 4% carbohydrates of total energy	Very restricted carbohydrate and limited protein intake. Very high in fat; therefore portion sizes will appear smaller.	Enteral fed patients as a complete formula feed is available. Those who are at nutritional risk.
Medium-chain triglyceride (MCT) ketogenic diet Fat: 70-75% (30%-60% MCT); 10% protein; 10-18% carbohydrates	Increased ketogenic potential of MCT means less total fat and more protein and carbohydrate, so a more varied diet (most generous carbohydrate allowance of all ketogenic therapies). MCT must be included at all meals and snacks and increased gradually during the diet initiation process to avoid risk of gastrointestinal side effects.	Children or adolescents who like a high carbohydrate intake or who are fussier about their food choices. Patients who are able to include the MCT supplement into their food and drink choices.
Modified Atkins diet (MAD) Fat 60-65%; 30% protein; 5-10% carbohydrates (10g children; 20g adults)	Free protein and energy without food weighing. Generous fat and protein choices. Very restricted carbohydrate intake. Controlled dietary energy intake to prevent excess weight gain.	Families, adolescents, and adults who prefer a less restrictive diet and who are able to design their own meals from the food choices given.
Low glycaemic index treatment (LGIT)	Dietetic guidance is needed to ensure energy requirements are met and advice is given on the	It is not as extensively researched as the classical and MCT options. Initial findings

Carbohydrate (40—60 g low GI CHO), protein (approximately 20%) and fat (high, approximately 50—60%) (limited to low glyceamic index carbohydrates).	type and amount of carbohydrate. The Glycemic Index of a food refers to how high that food raises your blood glucose after eating, compared to a reference food such as sugar. It is slightly higher in carbohydrates. This diet focuses on how carbohydrates affect the level of glucose in the blood (the glycaemic index), as well as the amount of carbohydrate eaten. Approximate portion sizes are used rather than food being weighed or measured.	indicate that it is an effective treatment for individuals with either generalized or partial onset seizures. Although research is still limited, children on the LGIT seem to have fewer side effects than with the traditional ketogenic diet. It may take a few months to see if the diet is effective.

DIETARY CONCERNS ASSOCIATED WITH THE USE OF ANTICONVULSANTS

Medications can affect nutritional status by interfering with the absorption, metabolism and excretion of nutrients in the food. When vitamins, minerals, or other food components alter drug utilization or when drugs induce nutritional deficiencies, the effect poses a risk to the patient. The management of epilepsy requires long-term care and drug therapy (anticonvulsants), frequently involving the use of multiple drugs. Anticonvulsant drugs such as phenytoin, phenobarbital, and primidone have been shown to induce clinical deficiencies of folate, biotin, and vitamin D.

According to the literature, the KD seems to enhance the anticonvulsant effects of valproic acid (VPA), carbamazepine, lamotrigine, and phenobarbitolephenobarbitale without affecting their pharmacokinetic and side effect profiles initiation, it is recommended to add the KD to the existing regimen of drugs, but to monitor patients when receiving the above mentioned anticonvulsants.

Summary of the interactions between anticonvulsant drugs and nutrients

1. Phenobarbitone (Trade names: Adco-phenobarb-vitalet, Gardenal, Garoin Norstan-Phenobarbitone)

Drug-nutrient interactions

Phenobarbitone has been shown to cause deficiencies of Vitamins D, B12, B6 and Folate as well as Calcium and Magnesium. Vitamin D deficiency may result in a decreased bone density, osteoporosis, rickets or osteomalacia. The decrease in serum (blood) folate and Vitamin B12 may cause megaloblastic anemia. The drug increases the excretion of Vitamin C in the urine and decreases the absorption of thiamin. Phenobarbitone may also cause appetite changes and is excreted in breast milk.

Dietary Suggestions

- Avoid alcohol consumption.
- Ensure an adequate exposure to direct sunlight.
- Eat a diet that includes good sources of Vitamin D (fish liver oils, butter, egg yolk, liver), folate (fresh green leafy vegetables, fruit, organ meats, dried nutritional yeast), Vitamin B12 (yeast, liver, beef, eggs, kidney), Vitamin B6 (yeast, organ meats, fish) and calcium (dairy products, nuts, oranges, broccoli). Include good sources of Magnesium (green leafy vegetables, nuts, and seafood).
- Absorption delayed by food, administrations of it needs to be staggered around mealtimes.

2. Phenytoin (Trade names: Epanutin and Garoin)

Drug-nutrient interactions

Phenytoin has been shown to cause deficiencies of Vitamins D, B12 and folate as well as Calcium and Magnesium. The deficiency of Vitamin D may result in a decreased bone density and cause rickets, osteoporosis or osteomalacia. The decrease in serum folate and Vitamin B12 may cause megaloblastic anemia. Phenytoin may cause constipation, nausea, vomiting and is excreted in breast milk. It may also increase blood glucose and dietary treatment might be necessary.

Dietary Suggestions

- Avoid alcohol consumption
- Ensure an adequate exposure to direct sunlight (Vitamin D is synthesized in the skin by exposure to direct sunlight).
- Eat a diet that includes good sources of Vitamin D (fish liver oils, butter, egg yolk, liver), folate (fresh green leafy vegetables, fruit, organ meats, dried nutritional yeast), Vitamin B12 (yeast, liver, beef, eggs, kidney), and calcium (dairy products, nuts, oranges, broccoli). Include good sources of Magnesium (green leafy vegetables, nuts, and seafood).

- Supplementation: 400-800 IU Vitamin D and 0.4-1 mg folic acid per day (consult with a doctor or dietitian).
- Take the drug with food or milk.

3. Carbamazepine (Trade names: Tegretol, Tegretol S, Prozine, Carpaz and Degranol)

Drug-nutrient interactions

There are indications that it may decrease serum (blood) levels of folic acid and Vitamin B12, however supplementation is only advised with confirmed low serum (blood tests) levels.

Dietary Suggestions

- Avoid alcohol consumption.
- Treat nausea, vomiting, abdominal pain, diarrhoea and constipation.

4. Ethosucximide (Trade name: Zarontin)

Drug-nutrient interactions

The drug decreases serum levels of Vitamin D. Other side effects: loss of appetite, nausea, vomiting, abdominal pain and anorexia. (Eat small frequent meals; Fluids should be taken between meals; Excess fat should be avoided; lightly flavored food is normally better tolerated).

Dietary Suggestions

- Avoid alcohol consumption.
- Treat nausea and vomiting and anorexia. (Eat small frequent meals; Fluids should be taken between meals; Excess fat should be avoided; lightly flavored food is normally better tolerated).

5. Sodium Valproate (Trade names: Convulex and Epilim)

Drug-nutrient interactions

The drug does not cause nutrient deficiencies, but may cause nausea, vomiting, diarrhoea and constipation. In general, these symptoms disappear after a while.

Dietary Suggestions

- Never take the drug on an empty stomach; eat a small meal or snack 10 – 20 min before taking this drug.

For further, personalized and more detailed information, please contact NICUS or a dietitian registered with the Health Professions Council of South Africa (HPCSA).

References from the scientific literature used to compile this document are available on request.

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