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MINI-REVIEW

Ketogenic diet: a therapeutic alternative in pediatric refractory epilepsies

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Abstract

Several studies have demonstrated the effectiveness of ketogenic diet (KD) on refractory epilepsies, especially in children. In this category of patients, a strong collaboration between the healthcare providers and the full engagement of parents is required. The regimen is significantly effective for different types of epilepsy that are resistant to medical treatment. It can also be used as a first-line treatment, given its well tolerance. Treatment has been rolled out for children but research into its use in adults is promising. There is no international or national protocol, the implementation of this diet follows a rigor being specific to every ketogenic center. The understanding of the underlying mechanisms is not well elucidated, it would make it possible to optimize the clinical use of the ketogenic diet, but also to develop novel antiepileptic treatments. This article aims to review the different variants of KD and their prescription terms in children with intractable epilepsy.

Keywords: drug-resistant epilepsy, ketogenic diet, children, Modified Atkins Diet.

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1 Introduction

Epilepsy constitutes a brain disorder characterized by a lasting predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition [1]. Epilepsy is a common pathology affecting 65 to 70 million people worldwide [2]. The management of this chronic disease aims to control seizures while preserving the patient's quality of life (QOL) [3]. Treatment is based on anti-epileptic drugs, which help control seizures in more than two-thirds of cases. Nevertheless, nearly one third of patients will continue to have seizures despite a well-conducted treatment, thus justifying the use of further therapies such as ketogenic diet (KD) or surgery [4].

KD is a high-fat (providing a range of 55 to 90% calories as fat), adequate protein (accounts for 30-35% of the daily caloric requirement supplied; minimum of 1 g/kg of protein), low-carbohydrate diet (only 5-10% of total calorie intakes are provided by carbohydrates, less than 50 g/day) [5]. The term KD currently refers to any dietary therapy which results in a metabolic ketogenic state. Ketones can result from the breakdown of fat; it is then an oxidation of fatty acids, secondary to a restriction in carbohydrates. Several studies have demonstrated the effectiveness of KD on refractory epilepsies especially in children [6]. Although KD is not a substitute for pharmacological treatments, it often reduces the number of antiepileptic drugs taken as combination therapy as well as their dosages [7]. This article reviews the different variants of KD and their prescription terms in children with intractable epilepsy.

2 Mechanism of action

Despite the use of KD for a hundred years, its antiepileptic mechanisms are not yet fully elucidated. The anticonvulsant effects of the KD have been studied primarily in rodent models exposed to electrical stimuli (e.g., pentylenetetrazol, maximal electroshock) [8] resulting in several hypotheses:

- The first mechanism proposed was the direct action of the ketone bodies, namely acetone, acetoacetate and β-hydroxybutyrate (BHB). Although many studies have attempted to establish a causal link between the blood level of BHB and the anticonvulsant effect of KD, no significant association has been demonstrated [9]. However, it is known that ketone bodies cause an overproduction of energy by the mitochondria. In addition, the ketogenic diet causes an increase in the number of mitochondria in the brain. This increase in energy capacity would stabilize synaptic transmission and raise the epileptogenic threshold [10]. Moreover, BHB appears to exert both epigenetic (inhibition of histone deacetylases) and anti-inflammatory activity. While these two effects of BHB have yet to be directly linked to epileptogenesis, parallel lines of evidence indicate that histone deacetylases inhibition and a reduction in neuroinflammation can block seizure activity [11];
- Another mechanism considered in relationship with the reduction in the use of glucose in the brain, which can lead to the activation of ATP-dependent potassium channels (Figure 1). The opening of these widely distributed channels in the central nervous system leads to neural membrane hyperpolarization, thereby reducing electrical excitability in the brain and raising seizure threshold [9];

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- The modulation of different neurotransmission systems is also suspected to be part of the mechanism of action of the KD, including those of monoamines, glutamate and γ-aminobutyric acid (GABA). Indeed, it has been observed that dopamine and serotonin concentrations are lowered in the cerebrospinal fluid of children with epilepsy treated with KD [12]. As for glutamate, which is the main excitatory neurotransmitter involved in the state of hyperexcitability encountered in epilepsy, its release by neurons would be reduced by acetoacetate which would have an inhibitory effect on the vesicular transporter VGLUT2 [13]. Conversely, the extracellular concentration of GABA, which is the main inhibitory neurotransmitter of the nervous system, could be increased by the KD through an alteration in the activity of enzymes for the synthesis and degradation of GABA [10].

A neuroprotective action of the KD is also being investigated. However, since diet-based therapy is likely to cause a wide range of biochemical, molecular, and cellular changes, it is highly probable that the systemic effects resulting from KD are not due to a single mechanism [7].

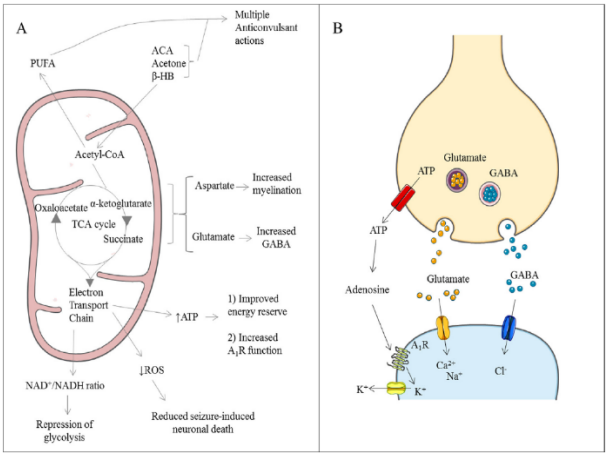

Figure 1: Multiple proposed anti-epileptogenic effects of the ketogenic diet involve the metabolism of ketone bodies in the mitochondria. A. products of mitochondrial metabolism of ketone bodies in neurons that are proposed to confer anti-epileptic effects. B. The effects of certain products from A on ion transfer at the synapse. A1R, adenosine A 1 receptor; ACA, acetoacetate; b-HB, beta hydroxybutyrate; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species [13].

3 Ketogenic diet and its variants

3.1 Classic ketogenic diet

Ketogenic diet is based on a particular weight proportionality between fat and the "non-fat" (carbohydrates and proteins) of the diet. Thus, if the diet provides four servings of fat for one serving of "non-fat", then the ratio is said to be "4: 1" [14].

There are other possible ratios: "1: 1", "2: 1", "3: 1" or "5: 1". The more ketogenic the calorie ratio, the more effective the diet, but tolerance is poor.

A study has shown that the "4: 1" ratio is more effective in reducing seizures than the "3: 1" ratio but tolerance is better for the "3: 1" ratio [15].

The rate of carbohydrate decreases depending on the type of diet selected. As the rate of protein is fixed for growth, the rate of vegetables and fruit is increasingly reduced [16]. However, particular diet should be adjusted to particular clinical situation.

The intensity of the diet depends on the age of the child:

- For children under 3 years old, a "3: 1" diet is preferred;
- For children over 3 years and adults, a "4: 1" diet is recommended provided that the protein intake allows an acceptable level of carbohydrate (more than 15 g per day) [17].

3.2 Modified Atkins Diet

This diet consists of a supply of fats and proteins without caloric restriction while the daily amount of glucose is limited. In addition, the proportion of fat and protein provided is less strict than in the classic ketogenic diet. It is recommended to start the diet with a daily carbohydrate intake of 10 g / day for the first three months. It is then feasible to increase depending on the clinical course to 20 g / day if the restriction is poorly tolerated [18]. This diet induces ketosis within four days without prior fasting [19] and has the advantage of being more permissive than the classic diet, thus improving compliance.

3.3 Diet with a low glycemic index

Food with a low glycemic index are food that are responsible for low changes in blood sugar and insulin levels. They are mainly represented by meats, certain vegetables and cereals [20]. The effectiveness of this diet in the treatment of epilepsy in both adults and children has been demonstrated by two studies [20, 21].

4 Indications

Ketogenic diet is an integral part of the therapeutic arsenal for refractory epilepsies which account for 20 to 30% of all epilepsies. It has been shown to be effective in a number of syndromes [22] such as West's syndrome (or infantile spasms) [23], myoclonic astatic epilepsy [24], Dravet syndrome [25] or even Lennox-Gastaut syndrome [26] and tuberous sclerosis of Bourneville [27].

Ketogenic diet is also a treatment for metabolic diseases such as glucose transporter deficiency (Glut-1 deficiency) or pyruvate dehydrogenase deficiency. In these two diseases, it is the unique treatment to have shown efficacy in providing the brain with an alternative energy source than glucose [28, 29].

5 Contraindications

The presence of any of the following issues precludes the establishment of KD: [30]

- Abnormalities in the oxidation of fatty acids;
- Deficiency of gluconeogenesis, ketogenesis;

- Pyruvate-carboxylase deficiency;
- Liver failure;
- Kidney disease;
- Diabetes mellitus Type 1;
- Pregnancy;
- Cardiac arrhythmias;
- Recent stroke or myocardial infarction;
- Heart failure;
- Respiratory failure;
- Malignancy;
- Non adherence to the diet.

A preliminary assessment is necessary to determine whether the initiation of KD is possible [31].

6 Drugs interactions

The combination of KD with certain antiepileptic drugs should be carefully monitored.

Patients on carbonic anhydrase inhibitors such as Topiramate or Zonisamide require careful monitoring because of the risk of kidney stones [32].

There are no formal contraindications with performing general anesthesia in patients on a ketogenic diet. However, there is a precaution for use with respect to a particular anesthetic, propofol, with which a case of death has been observed [33, 34].

There is no benefit in modifying the dosage of antiepileptics because KD has been shown not to modify their plasma levels [35]. On the other hand, the effectiveness of KD can allow a reduction in the dosage of antiepileptics or even a discontinuation.

7 Implementation of ketogenic diet

The implementation of KD in children must be initiated in a hospital environment under the close supervision of a well-trained team in order to ensure optimal education of the family [36]. The child's eating habits are evaluated by the dietitian who will judge the feasibility of the diet and who will instruct the parents on the importance of good compliance with the diet and intolerance signs. These signs are mainly observed in infants and are mainly represented by hypoglycemia and hyperketosis [36].

Hypoglycemia is manifested by restlessness, hypotonia, lethargy, skin pallor, and even hypothermia with cyanosis. Hyperketosis clinically manifests as polypnea, tachycardia, skin flushing, irritability, vomiting with the odor of acetone.

Some teams initiate the diet with an initial fasting period of 24 to 48 hours to achieve faster seizure control, particularly in pediatric intensive care in the context of status epilepticus [37].

The international Ketogenic Diet study group recommends laboratory tests before starting the diet [38] (Table 1). During the first days of the diet, monitoring of capillary glycemia and the presence of urinary ketone bodies is required several times a day[39].

Table 1: Laboratory examinations before ketogenic diet initiation [38]

Required exams	Glycemia and vitamin D
	Blood count and platelets
	Blood serum ionogram
	Bicarbonates
	Plasma proteins
	Calcium, Magnesium, Phosphate
	Hepatic tests (albumin, ASAT, ALT)
	Kidney function (urea, creatinine)
	Lipid profile
	Plasma acylcarnitine profiles
	Calciuria and creatininuria,
	Chromatography of urinary organic acids
Recommended exams	Vitamins A, E, B12, Zinc
Optional exams	Renal ultrasound if family history of renal lithiasis
	Electroencephalogram
	Magnetic resonance imaging
	Cerebrospinal fluid analysis
	Electrocardiogram

8 Efficacy

The diet's effectiveness has been demonstrated by two randomized trials: one for the classic ketogenic diet and one for the modified Atkins diet [37, 40].

The effectiveness of KD is assessed by the reduction in the frequency of seizures, which is a priori not correlated with ketonuria or ketonemia [41]. The antiepileptic effect of the modified Atkins-type or low glycemic index ketogenic diet appears to be comparable to that of the "4: 1" ketogenic diet [42].

It is possible that other positive effects of diet exist, particularly on behavior and cognition. It has been suggested that in addition to its effect on seizure frequency, the ketogenic diet may also improve attention and cognitive functions [43].

After the introduction of the ketogenic diet, 75% of children are responders at 14 days and 90% at 23 days. In the long term, 75% of children have a reduction of more than 50% of seizures and 48% see their frequency of seizures decrease by more than 90% at 3 months [44].

9 Duration of the ketogenic diet

It is recommended to maintain the ketogenic diet for at least 3 months before judging its effectiveness. When it is effective, it is followed up for 2 years with the possibility of gradually increasing the proportion of carbohydrates [39].

The diet is stopped approximately after two years in children whose number of seizures has decreased by more than 50% and can be continued until 6 to 12 years for responders over 90%, in the absence of adverse effects [45].

10 Follow up

Children on a ketogenic diet should be monitored regularly, both by the dietitian and by the neurologist. Initially, the children are seen every 2-3 months and then after one year of diet the monitoring is spaced every six months.

At each visit, body weight, height, and head circumference should be measured to track growth. The treatment should be reassessed as well as compliance with the regimen, its effectiveness (seizure schedule, behavior), its tolerance and any adverse effects [46].

11 Side effects

The most encountered side effects are gastrointestinal disorders (12–50%) such as constipation, diarrhea, vomiting and abdominal pain [47]. Constipation can be treated with a higher fiber diet and laxative treatments. Vomiting may be due to gastroesophageal reflux or hyperketosis. This may require the setting up of a rehydration. A few cases of pancreatitis and hepatitis have also been reported [48].

In case of abdominal pain, beware of the risk of renal lithiasis which may be increased by taking certain antiepileptics such as Topiramate or Zonisamide. This risk is 2-6% and can be as high as 25% for a KD of six years or more [49]. Some teams supplement with potassium citrate, which would reduce the risk of kidney stones by 9% [50].

At the metabolic level, the main side effects are hypoglycemia, metabolic acidosis (2-5%), hyperuricemia (2-26%), hypocalcemia (2%), hypomagnesemia (5%) and hyperketosis. In case of symptomatic hypoglycemia, the child should be given sugar [39]. Vitamin deficiencies are also described, which therefore require supplementation with calcium and vitamin D in order to limit the risk of osteoporosis and delayed weight [39].

At the cardiovascular level, KD can also lead to hypercholesterolemia [51], hyper-triglyceridemia and elevated apolipoprotein B [6]. Isolated cases of cardiomyopathy or ECG-corrected QT interval prolongation have been reported [6].

KD is also associated to higher incidence of renal calculi which can be prevented by prescribing 2 mmol potassium citrate/kg/day for the duration of treatment [52].

Long-term complications are mainly represented by bone fractures and height stagnation. It is therefore recommended to perform a regular bone densitometry [6].

12 Conclusions

Ketogenic diet and its variants are safe and effective among children with drug resistant epilepsy. This latter completely escapes the conventional therapies available today and its management is very complex. Ketogenic diet thus constitutes an interesting alternative in the face of ineffective drug combination therapy. The ketogenic diet is a therapeutic option in the treatment of drug-resistant epilepsies and certain epileptic syndromes in children. It constitutes also the first-line treatment of certain metabolic diseases such as glucose transporter deficiency of the GLUT1 type or pyruvate dehydrogenase deficiency. There are different types of ketogenic diets including the modified Atkins diet which seems less restrictive than the classic ketogenic diet. It is essential to know the absolute and relative contraindications of the diet and its complications in order to prevent them.

Given the beneficial clinical outcomes regarding efficacy and safety, KD should be considered as a treatment option for children with refractory epilepsy who are not eligible for epilepsy surgery.

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