

To treat or not to treat drug-refractory epilepsy by the ketogenic diet? That is the question

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Ułamek-Kozioł M, Pluta R, Bogucka-Kocka A, Czuczwar S J. To treat or not to treat drug-refractory epilepsy by the ketogenic diet? That is the question. *Ann Agron Environ Med.* 2016; 23(4): 533–536. doi: 10.5604/12321966.1226841

Abstract

Epilepsy is a serious neurologic disorder worldwide which affects about 1% of the population (ca. 50 million people), the highest prevalence occurring in both children and elderly. Apart from idiopathic forms, etiology of the disease involves multiple brain risk factors – the most frequent being cerebrovascular diseases, tumours and traumatic injuries. Several treatment options exist, including, for instance, pharmacotherapy, vagal nerve stimulation or epilepsy surgery. In spite of treatment, about 30% of patients with epilepsy still have seizures and become drug-refractory. This is why other treatment options may be recommended, and ketogenic diet seems a last-chance method, especially in children and adolescents with epilepsy. The diet contains high amounts of fat and low carbohydrates with vitamin supplementation. The elevated concentrations of ketones induced by the diet may result in inhibition of the synaptic activity of glutamate, the mammalian target of the rapamycin pathway, and activation of adenosine triphosphate-sensitive potassium channels. One of the main ketones is acetone, shown to increase the seizure threshold and potentiate the anticonvulsant activity of some antiepileptic drugs. The clinical effectiveness of the ketogenic diet has been confirmed in a number of clinical trials carried out mainly on children. A wider use of the ketogenic diet may be limited by the number of early adverse effects (gastrointestinal distress, acidosis, hypoglycaemia, dehydration and lethargy), and late adverse effects (hyperuricaemia, hyperlipidaemia, kidney stones, easy bruising, and decreases in height and weight). Recently, data are available on the negative impact of the ketogenic diet on the qualitative characteristics of lipoprotein subfractions which points to the atherogenic phenotype as a new side-effect. In conclusion, future research directed to the proper identification of patients (in terms of age, epilepsy type and duration, recommended antiepileptic drugs) is necessary to answer the title question.

Key words

ketogenic diet, ketones, acetone, epilepsy, antiepileptic drugs

INTRODUCTION

Epilepsy is a serious and expensive health problem worldwide [1] and accounts for estimated direct and indirect costs annually of about €15.5 billion in Europe [2] and \$15.5 billion in the United States [3]. In addition, epilepsy is the most frequent and devastating neurologic disorder in the world, with an estimated prevalence of 1% of the population [4, 5], affecting 50 million people, 80% of whom live in poor countries [6]. The highest prevalence occurs in both children and elderly, with low frequency in early adulthood [7]. Different kinds of brain lesions and injuries are involved in an increased risk for the generation of epilepsy. Epileptogenesis is a cascade of events, following genetic mutations, brain infections, traumatic brain injury or status epilepticus, which eventually lead to a conversion of normal into an epileptic brain [8]. Brain alterations are frequently followed by a latent phase of variable length before the appearance

of clinical symptoms. The latent stage is characterized by different neurochemical and neuropathological alterations in the brain, such as neuronal necrosis, apoptosis, axonal sprouting, synaptogenesis and induction of gene expression [9, 10]. Early symptomatic seizures develop at the time of the brain damage and are the marker of a severe injury. Epilepsy is a widespread and life-threatening neurological disease characterized by spontaneous sudden, irregular and abnormal neuronal discharges. Epilepsy is characterized by seizures that reflect a repeated neuropathological and uncontrolled electric activity in one or a few regions of the brain [11]. The etiology of epilepsy is complex and associated with multiple brain risk factors, the most common including cerebrovascular diseases (21%), tumours (11%), traumatic brain injuries (7%), and others like toxic and infectious disorders, congenital malformations, and genetic alternations [9, 10]. The development of epileptic neuropathology causes cognitive, psychological and social consequences [11]. The neuropathological mechanisms of epilepsy are only partly understood and may include a general neurochemical and blood–brain barrier dysfunction, generation of free radicals and the release of excitotoxins, such as glutamate, and alternations in energy metabolism [9]. Such a neuropathology is believed to be the end result of long-term alterations in the brain neuronal network [9].

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Received: 07 September 2016; accepted: 09 November 2016

Classic epilepsy therapy includes pharmacologic treatment, vagal nerve stimulation and epilepsy surgery. Despite these therapies, around 30% of patients with epilepsy are not sufficiently controlled and become drug-refractory [7]. This is defined as an insufficient control of seizures despite an optimal therapy with a combination of 2 or even more properly selected antiepileptic drugs [12]. Patients with drug-refractory epilepsy depend on informal family and friends' care, and on healthcare professionals, such as neurologists, psychologists, social workers, etc. Complications due to drug-refractory epilepsy in children and adolescents result in repeated hospitalizations and the institutionalization of many patients. Living with uncontrolled epilepsy has a harmful impact on the quality of the lives of the children and their caregivers.

Ketogenic diet. Ketogenic diet therapy should be considered in patients who have insufficiently responded to the therapy of two well-selected and well-dosed antiepileptic drugs [13]. In these circumstances, adding extra antiepileptic drugs frequently does not result in considerable seizure reduction. This is why other therapies, such as diet, including the ketogenic diet, are often recommended by medical neurologists to place the patients under better control [9, 14]. The ketogenic diet is a last-chance treatment for many children and adolescents with epilepsy. Although epilepsy study is flourishing, the mechanisms of this disorder have not yet been completely solved, and fully effective treatments in all patients with epilepsy have not been discovered to date. Epilepsy is a top priority for many pharmaceutical companies, making epilepsy one of the most investigated brain disorders in the pharmaceutical industry. It should be realized that in spite of the annual development of new antiepileptic drugs, the treatment, as already mentioned, in about one-third of epileptic subjects is not fully effective [15, 16]. For numerous refractory epilepsy patients, a dietary treatment offers hope for an improved quality of lives with a considerable decrease in seizure frequency. For this reason, an increase of the worldwide use of the ketogenic diet is observed at the moment [17]. A successful realization of this dietary therapy depends on active support from a healthcare team, social and educational system, and finally the family [17]. The ketogenic diet requires a strict dietetic and medical control because of its restrictiveness and side-effects (Tab. 1) [13].

Ketogenic diet – mechanisms of action. As its principal working mechanism has not yet been fully understood, it is not clear which patients benefit most [18]. One of the probable working mechanisms of the ketogenic diet is inhibition of glutamatergic excitatory transmission in synapses [19]. Ketones block glutamate transport into synaptic vesicles. Other mechanisms include carbohydrate reduction, activation of adenosine triphosphate-sensitive potassium channels by mitochondrial metabolism, and inhibition of the mammalian target of the rapamycin pathway [20]. It is certain that one of the main ketone bodies derived from the diet is acetone, exerting a clear-cut anticonvulsant activity against pentylenetetrazol- or 4-aminopyridine-induced seizures in mice, and at the effective anticonvulsant doses, the ketone produced no motor impairment [21]. Probably, the protective activity of acetone is not associated with its metabolites, acetol, 1,2-propanediol or pyruvic acid

Table 1. Side-effects in children with drug-refractory epilepsy treated by ketogenic diet [4,7,29,32-35,40]. Modified and updated from Lee and Kossoff [41]

Early side-effects	Late side-effects	Rare side-effects
Acidosis	Alternations in apolipoprotein B	Allergy
Constipation	Alternations in arterial function	Basal ganglia changes
Dehydration	Atherogenic phenotype	Cardiomyopathy
Exacerbation of gastroesophageal reflux disease	Bone fractures	Oesophagitis
Excessive ketosis	Bruising	Fanconi's renal tubular acidosis
Fatigue	Decreased bone mineral density	Gallstones
Food refusal	Dyslipidaemia	Hepatitis
Gastrointestinal distress	Hyperuricaemia	Hypocalcaemia
Hypoglycaemia	Kidney stones	Hypomagnesaemia
Increased seizure frequency	Poor growth	Hyponatraemia
Lethargy	Secondary carnitine deficiency	Hypoproteinaemia
Vomiting	Vitamin D deficiency Vitamin, mineral and enzyme deficiencies, Weight loss	Increased illnesses Selenium deficiency Lipoid pneumonia Sudden death

[21]. Interestingly, this ketone body could also affect the anticonvulsant activity of a number of antiepileptic drugs against maximal electroshock-induced seizures in mice. When administered in subprotective doses against maximal electroshock seizure threshold tests, it efficiently potentiated the protective activity of carbamazepine, phenobarbital, valproate (classic antiepileptic drugs) and lamotrigine (a newer antiepileptic drug) against maximal electroshock-induced convulsions in mice with the use of supra-maximal current intensity. Pharmacokinetic interactions between acetone and antiepileptics seem unlikely because the ketone did not modify the total brain concentrations of the affected antiepileptic drugs. However, the anticonvulsant activity of some antiepileptic drugs was not influenced by acetone – these are phenytoin (a classic antiepileptic) and both, oxcarbazepine and topiramate (newer antiepileptic drugs) [22]. Apart from acetone, other constituents of the ketogenic diet may also be taken into consideration in terms of the anticonvulsant activity. For instance, caprylic acid (an 8 carbon fatty acid, present in the medium-chain triglyceride ketogenic diet) elevated the threshold for 6 Hz psychomotor seizures in rodents, but was ineffective as regards the maximal electroshock threshold seizure test. It is noteworthy that caprylic acid, although ineffective against electroconvulsions, significantly enhanced the protection offered by valproate against maximal electroshock-induced seizures in mice, without any involvement of a pharmacokinetic mechanism. This positive interaction was also noted against 6 Hz-induced convulsions in mice [23]. Another constituent of the medium chain triglyceride ketogenic diet, capric acid, a 10-carbon fatty acid, has also been found to be effective against a number of convulsive tests in mice – maximal electroshock seizure threshold, 6 Hz seizure threshold and intravenous pentylenetetrazol seizure tests [24]. Recently, an intriguing hypothesis has appeared that caprylic and capric acid elevated

the brain concentration of tryptophane, as well as the central and peripheral level of kynurenic acid. Interestingly, when the passage of tryptophane into the brain was prevented, the anticonvulsant activity of these fatty acids disappeared [25].

Clinical effectiveness and adverse effects. The ketogenic diet is high in fat and low in carbohydrates, and has an adequate amount of protein for growth, usually at a 4:1 fat to protein ratio, carbohydrates plus required vitamin supplementation [4, 5]. The ketogenic diet has been proved to be useful in children with epilepsy by a meta-analysis study and in randomized controlled trials: 15% of patients became seizure-free and 33% reached a 50% decrease in seizure frequency [26–29]. If a reduction in seizure frequency is reached, antiepileptic drug therapy decrease can be taken into account after 3–6 months. Patients usually stay on the diet for 1–2 years before discontinuation is considered [30]. A recent study of the ketogenic diet in adults with refractory epilepsy has additionally demonstrated a high efficacy and tolerability [31]. Firstly, there was a lot of enthusiasm because patients tolerated the therapy very well, without dangerous side-effects. Fast enthusiasm went down because of early noted side-effects which included gastrointestinal distress, acidosis, hypoglycaemia, dehydration and lethargy (Tab. 1) [7, 29, 32–34]. Late side-effects, including hyperuricaemia, hyperlipidaemia, kidney stones, easy bruising, and decreases in height and weight were additionally observed (Tab. 1) [7, 32–34]. Also, decreased bone density and bone fractures were frequently noted [7, 32–34]. Deaths were recorded in children during the ketogenic diet therapy, while it is not clear whether any of the noted deaths were directly associated with using the ketogenic diet [7, 32, 33]. Side-effects of the ketogenic diet from time-to-time necessitated stopping the treatment because of anaphylaxis (Tab. 1) [4], and it is very important for pediatric neurologists to recognize this. Nowadays, use of the ketogenic diet treatment for children and adolescents with intractable epilepsy continues to grow in attractiveness, both from clinical and research point of view. Recently, de Lima et al. [35] suggested that the diet had an atherogenic end result on the physical properties of lipoproteins subfractions, regardless of the positive effect of the ketogenic diet therapy on refractory seizure control in children and adolescents. Their data confirmed the positive clinical effect of the ketogenic diet therapy on refractory epilepsy, the effect of which is unquestionable. However, they stressed the negative impact of the diet on the qualitative characteristics of lipoprotein subfractions. Following use of the ketogenic diet, the percentage of small LDL increased, and both the LDL size and percentage of small HDL decreased. The ketogenic diet caused development of atherogenic phenotype in patients: 3 and 6 months following the treatment, and was evident in 31% and 52% of cases, respectively. In another study, the initial alterations in lipids, apolipoprotein B and arterial function observed within the first year of the ketogenic diet therapy were found to be reversible, and not significant after 2 years of therapy [36]. The dyslipidaemia observed after ketogenic diet therapy is associated not only with the ketogenic diet, but also with the drugs used during the treatment of epilepsy [37]. The atherogenic side-effect observed by de Lima et al. [35] seriously challenges the use of the ketogenic diet therapy for refractory epilepsy. In 2015, de Lima et al. [38] also predicted that such a therapy probably contributed to changes in the size of lipoproteins, particularly

related to small LDL. In their recent study, they highlighted for the first time the importance of monitoring not only the classic lipid profile, but also the size of lipoprotein subfractions [35]. An important change in the mindset of neurologists and dietitians at ketogenic diet centres is now to prevent these negative side effects before they actually occur. Finally the authors suggested some practical observations for clinicians [35]: *First, use a modified ketogenic diet, with fewer atherogenic fatty acids. Second, initiate coadjuvant ketogenic diet treatment early to reduce the number and quantity of antiepileptic drugs that show dyslipidemic action. Finally, include lipoprotein size in routine laboratory examinations in addition to the classic lipid profile* [35].

CONCLUSIONS

The study by de Lima et al. [35], however, has some limitations. The number of individuals investigated was relatively small, although the number of measurements made was quite large and the differences clearly present. Future investigations also need to determine ways on how to improve the quality of the lives of patients in the later course of the illness. Effective integration is needed of these new side-effects with the known heterogeneity of refractory epilepsy. It is probable that this study should have had a control group with healthy patients versus the ketogenic diet, and the patients without antiepileptic drugs but also with the ketogenic diet [39]. The investigated group should be more homogeneous in age. The researchers should also investigate the vascular function using, e.g. carotid ultrasound in the future. However, the Lima's et al. [35] study sheds new light on the complex relationship between the ketogenic diet therapy and refractory epilepsy; it also generates a number of questions that need to be answered. Is this treatment a really safe therapy? What facts continue to speak in support of the ketogenic diet treatment? Obviously, regardless of the early enthusiasm for the ketogenic diet therapy, we are still in the early stages of safe use and understanding it. We should draw conclusions from the study by de Lima et al. [35] and return to the bench to do our homework before negative side-effects can be noted. This study should also serve as a fresh starting point for clinicians interested in developing the ketogenic diet as an alternative therapy for the refractory epilepsy. This approach should be perceived as a new ground for the design and implementation of clinical research to help answer some of the numerous questions remaining. We can add an atherogenic reaction to the dangerous risk side-effects of the ketogenic diet treatment. For this goal, larger multicentre studies are needed. Future research should focus on identifying patients (according to age, type and duration of epilepsy, drug therapy, etc.) who benefit the most from the ketogenic diet. Can refractory epilepsy be treated by the ketogenic diet? Currently, this question has no answer; we can only add the atherogenic phenotype to new side-effects.

Acknowledgements

The authors acknowledge the support provided by the Mossakowski Medical Research Centre, Polish Academy of Sciences, Poland (T3-RP), and by the statutory grants from the Institute of Rural Health and the Medical University in Lublin, Poland (SJC).

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