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KETOGENIC DIET AND EPILEPSY: A NARRATIVE REVIEW OF THE LITERATURE

A.R.
ARTIGO DE REVISÃO

DIETA CETOGÉNICA E EPILEPSIA: UMA REVISÃO NARRATIVA DA LITERATURA

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ABSTRACT

Several studies have already explored the role of ketone bodies on the physiological processes involved in the onset of seizures and ketogenic diet is a common treatment option in drug-resistant epilepsy either in children, adolescents or adults. This narrative review aims to summarize the available evidence on the possible mechanisms of action, and on the efficacy of the ketogenic diet and its variants on the treatment of epilepsy from infants to adults. Even though there is a robust biologic plausibility and either mechanistic studies and randomized controlled trials supporting ketogenic diet as a valid approach to reduce seizures in drug-resistant childhood epilepsy, the level of evidence is not as strong for the treatment of drug-resistant epilepsy in adults.

KEYWORDS

Epilepsy, Ketone bodies, Ketogenic diet, Seizures

RESUMO

Vários estudos têm explorado o papel dos corpos cetónicos nos processos fisiológicos envolvidos no despontar de convulsões sendo a dieta cetogénica uma opção de tratamento usual na epilepsia fármaco-resistente, quer em crianças, adolescentes ou adultos. A presente revisão narrativa procura resumir a evidência disponível sobre os possíveis mecanismos de ação e eficácia da dieta cetogénica e suas variantes no tratamento da epilepsia de crianças a adultos. Apesar da forte plausibilidade biológica e da existência de estudos mecanicistas e ensaios clínicos controlados e aleatorizados que suportam a dieta cetogénica como uma abordagem válida para reduzir a probabilidade de convulsões na epilepsia fármaco-resistente em crianças, o nível de evidência não é tão forte para a sua utilização no tratamento de adultos.

PALAVRAS-CHAVE

Epilepsia, Corpos cetónicos, Dieta cetogénica, Convulsões

INTRODUCTION

Epilepsy is a neurological disorder characterized by seizures, which affect about 70 million people worldwide (1). Almost one-third of patients with epilepsy continue to have disabling seizures despite the treatment with anti-seizures drugs (2). The International League Against Epilepsy defines drug resistant epilepsy as a failure of adequate trials of two tolerated and appropriately chosen and dosed epileptic drugs (whether as monotherapies or in combination) to achieve sustained seizure freedom (3). Resective epilepsy surgery is a possibility for patients with drug resistant epilepsy, but, in a proportion of drug resistant epilepsy patients, resective surgery might not be an option (2), and Ketogenic diet (KD) therapies are used as an established non-pharmacologic alternative (3). Following a KD requests careful dietary planning with balanced macronutrient proportion in order to achieve ketosis (4). Supported in the alterations of metabolic processes due to the increase of ketone bodies, multiple papers are now available on the effect of the KD on seizures in epileptic patients. Therefore, this review aims to summarize the mechanisms which supports the role of KD on epilepsy management and to condense the available evidence on the effectiveness of KD on seizures prevention on epileptic human subjects.

METHODOLOGY

The entire review was conducted on the basis of a PubMed search with no date restrictions and aiming mainly to identify mechanistic studies and randomized controlled trials, using the keywords 'ketone bodies', 'ketogenic diet' and 'epilepsy'. After analysing the title and sometimes the abstract of the 322 articles identified, 35 were integrated in this review.

History and Origins

Fasting and other diets have been used to treat epilepsy since 500 BC (5), but only in 1921, Woodyatt observed that

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in healthy subjects, starvation or a diet containing a low proportion of carbohydrates and a high proportion of fat, increased acetone and beta-hydroxybutyric levels in the blood. Wilder proposed that a KD should be tested in patients with epilepsy. He suggested that the KD could be as effective as fasting, but likely to be maintained long-term. Wilder subsequently coined the term KD to the ketone-producing diet (5).

In 1925 Peterman proposed a macronutrients ratio for the KD, still accepted nowadays: 1 g of protein per kilogram of body weight in children, 10–15 g of carbohydrates per day, and the remainder of the calories in fat (5).

In 1972 Livingston, at Johns Hopkins Hospital, based on the results obtained using KD in over a thousand children with epilepsy, showed that 52% achieved seizures freedom 27% had improved seizures (5).

In 1938, Merritt and Putnam discovered diphenylhydantoin, and the KD popularity, as a therapeutic diet for pediatric epilepsy ceased with the introduction of antiepileptic drugs (5).

Historically, the classic KD is a very low-carbohydrate with moderate-protein and high-fat diet, composed of a 4:1 ratio (4 g of fat to every 1 g of protein and carbohydrate) (2). Although KD is currently used in clinical practice, its application requires detailed calculation, education, and training, precise food weighing, and careful food preparation (6). Therefore, with the aim of improving compliance to KD, the modified Atkins diet is often used as a modification of the classic KD, always with defined protocols (6). The modified Atkins diet is typically composed of a net 10-20 g/day carbohydrate limit, equivalent to a ratio 1-2:1 of fat to protein and carbohydrates (2).

A hybrid between the classic KD and the modified Atkins diet is called the modified KD, where carbohydrates provides around 5% of the total energy intake (approximately 20-30 g/day) and fat provides about 75%. This strategy offers the dietary control offered by the classic KD and the flexibility of modified Atkins diet (6). This variants aim to increase the variability, the palatability, and the tolerability of the diet, improving the compliance, an important factor for a successful dietary treatment (7).

It seems that, after a few days with such drastically reduced carbohydrate consumption, glucose reserves become insufficient, both for normal fat oxidation through the supply of oxaloacetate in the Krebs cycle and for the supply of glucose to the central nervous system. The central nervous system cannot use fatty acids as a nutritional source. Hence, after 3-4 days of carbohydrate restriction, the central nervous system is forced to find an alternative energy source: ketone bodies (8).

Biochemistry of Ketone Bodies

Ketogenesis, starting either from fatty acid oxidation or oxidation of ketogenic amino acids, leads to the formation of ketone bodies, three distinct molecules known as β-hydroxybutyrate, acetoacetate, and acetone. They represent circulating energy molecules during fasting or prolonged exercise. Most of the biosynthetic process occurs in the mitochondria of the hepatocytes, even though a small production may be found in other tissues, like kidney epithelia, astrocytes, and enterocytes (9).

In the initial phase of fasting, tissues rely primarily on glucose metabolism, and glycogen stored in muscle and liver is depleted first. After a prolonged fast, fatty acids are mobilized from the adipose tissue to the liver, and they undergo β-oxidation to produce acetyl-CoA that enters the tricarboxylic acid cycle (Krebs cycle). Under normal conditions, acetyl-CoA from fatty acid β-oxidation is further oxidized via the tricarboxylic acid cycle, and then, the reduced coenzymes NADH and FADH2 allow the production of energy by the electron transport chain in the mitochondria coupled to ATP synthesis (oxidative phosphorylation, OXPHOS). However, the tricarboxylic acid cycle cannot handle the large amount of acetyl-CoA derived from fatty acid β-oxidation due to low levels of insulin, the increase of the fatty acids release and of the enzymes required for ketone body synthesis and utilization. Simultaneously, the diversion of oxaloacetate to feed gluconeogenesis in the liver leads to low activity of TCA cycle due to reduced amounts of metabolic intermediates, which increases acetyl-CoA levels that increases its usage as a substrate for ketone body synthesis (10). Acetyl-CoA derived from fatty acid β-oxidation is the substrate for the first step of ketogenesis: acetoacetyl-CoA thiolase (ACAT1) catalyzes the condensation of two molecules of acetyl-CoA to form acetoacetyl-CoA. Mitochondrial hydroxymethyl glutaryl-CoA synthase (HMGCS2), the rate-limiting enzyme of the pathway, promotes the addition of a third acetyl-CoA molecule to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). The first ketone body, acetoacetate, is then produced by HMG-CoA lyase (HMGCL). ACA is the common precursor of the other two ketone bodies: it is mainly reduced to βOHB by NADH-dependent β-hydroxybutyrate dehydrogenase (BDH). The third ketone body derives from the spontaneous decarboxylation of ACA in a volatile product, acetone, which is excreted mainly through the lungs (11).

Regulators of Ketogenesis

Higher levels of insulin strongly inhibit ketogenesis, even when catabolic hormones are also secreted. Insulin acts in two complementary manners: first, it blocks lipolysis in adipocytes; and, it promotes glucose uptake and oxidation by tissues, which results in elevated succinyl-CoA and malonyl-CoA levels. These intermediates are potent inhibitors of fatty acid oxidation and ketone body formation in the liver and other ketogenic tissues. When insulin levels are low, the catabolic hormones, namely glucagon (secreted by the pancreas), cortisol, catecholamines, epinephrine, norepinephrine, and thyroid hormones, come into prominence (12, 13).

Ketogenic Diet Mechanisms in Seizure Managment

In a diet rich in carbohydrates, glucose is the 'preferred' substrate by the brain to obtain energy, in the KD the situation changes. The ingested fatty acids are metabolised in liver mitochondria into ketone bodies which are then released into the blood stream and are taken up by multiple organs including the brain. In the mitochondria of neurons and glial cells ketone bodies are catabolised to acetyl-CoA, which can then enter the TCA cycle for energy generation (producing NADH and ultimately ATP), or it can be used in lipogenesis to produce fatty acids. A consequence of the increased dependence on mitochondria for energy generation with the KD is that the numbers of that organelle increase in neurons and glia (12).

ATP and energy metabolism are intimately connected to another process through which the KD is involved in neuroprotective mechanisms, proposed to increase the seizure threshold and to reduce the damage to the brain that is generated by seizures. (14) As mentioned above, KD leads to mitochondrial biogenensis (13) probably because of the importance of the mitochondria for energy generation from fat, increasing ATP production capacity which is used to full Na/K-ATPase and other pumps, which serve to stabilize neuronal membrane potential (13).

Reactive oxygen species (ROS) formation occurs when unpaired electrons escape the electron transport chain and react with molecular oxygen; ROS increase causes cell damage and death (15). An increase of ROS is observed at onset of KD, followed by a decrease when the diet is prolonged at least one week, thanks to the involvement of the Nrf2 pathway and to stimulation of glutathione production (14). The above improves neuronal homeostasis and reduces the impacts of the high energy drain during seizures (15).

The increase in the biosynthesis of different fat products in patients on a KD provide other neuroprotective mechanisms. Hypomyelination is a feature of some epilepsies and a KD increases brain levels of acetyl-CoA (from ketone bodies) and aspartate (from TCA-cycle intermediates) which both contribute to the synthesis of myelin (16). Another product of fat

metabolism with probable anti-seizure effects is poly-unsaturated fatty acids which can be higher in the brain of patients on a KD and they are thought to protect neurons through simulating mitochondrial uncoupling proteins which reduce reactive oxygen species production, and poly-unsaturated fatty acids can also directly modulate different types of ion pumps and channels thereby reducing neuronal hyperexcitability (17).
There is also evidence that the decrease in glycolysis in patients on a KD contributes to the improved seizure control, in fact, there is a rapid resumption of seizures when patients on a KD resume ingesting carbohydrates or glucose (18), these effects may be linked to reductions in lactate (which is produced by glycolysis) which can alter neuronal membrane polarity through ATP-dependent potassium channels (19).
Ketone bodies may also alter the behaviour of vesicular glutamate transporters (VGLUTs). Cl^- acts as an allosteric activator of VGLUT and triggers glutamate uptake upon binding. Ketone bodies compete for the putative Cl^- binding site(s) and turn VGLUT activity off upon binding, causing a reduction in glutamatergic neurotransmission in vivo (20, 21).

Evidence in Children and Adolescents

KD has been successfully used in drug-resistant epilepsy, and research has shown that this diet is more successful at younger age in achieving seizure freedom (22).
Many studies have shown that children and adolescents following a KD have a 50% reduction in seizure frequency, which is considered as clinically relevant (23).
Based on the current guidelines for infancy and the high capacity of achieving ketosis in infancy, a fat/non-fat ratio of 3:1 is recommended (22).
In 2016 Kim and colleagues compare the efficacy, safety, and tolerability of a modified Atkins diet with the classic KD for the treatment of drug-resistant childhood epilepsy, and showed that the modified Atkins diet might be considered a good treatment, but the classic KD is more suitable in patients under two years of age (24).
The treatment with KD and modified Atkins diet was effective in children with refractory epilepsy of genetic etiology with responder rates at 1, 3, 6, 12, and 24 months being 63%, 61%, 54%, 53%, and 41% respectively (3).
A recent cohort study evaluated the efficacy and safety of KD for children with refractory epilepsy and despite the low compliance with the recommended distribution of macronutrients and the reported lack of palatability of the diet, the antiepileptic effect of the treatment was confirmed. There were 139 patients included in this study and at 1 month' follow-up, 39 of 139 (28.0%) subjects were responders: 9 (6.5%) were seizure-free, 12 (8.6%) had a seizure reduction of >75%, and 18 (12.8%) had a seizure reduction of 50–75%. At 3 months' follow-up, 71 of 129 (55%) subjects were responders: 17 (13.2%) were seizure-free, 23 (17.8%) had a seizure reduction of >75%, and 31 (24.0%) had a seizure reduction of 50–75%. At 6 months' follow-up, 70 of 103 (67.9%) subjects were responders: 24 (23.3%) were seizure-free, 16 (15.5%) had a seizure reduction of >75%, and 30 (29.0%) had a seizure reduction of 50–75% (25). In fact, a recent meta-analysis (26) which aimed to assess whether spasm remission during the period of 3 months KD can be a prediction index for the therapeutic effect of 6 months treatment, showed that a period of 3 months KD can be a prediction index of 6 months duration in term of spasm remission.
Baby and colleagues reported the efficacy and tolerability of KD in a series of 74 South Indian children with refractory epilepsy during 5 years. The results were that 44 children reported a seizure reduction higher than 50%. Among these, 19 children reported seizure reduction between 50 and 90%, 25 children more than 90% of seizure reduction and 6 children (8.1%) achieved seizure freedom during the maintenance phase (27).
Ketogenic treatment in children is safe, without significant adverse reactions, but can lead to micronutritional deficits as selenium (23).
In recent meta-analysis (1) regarding the efficacy and tolerability of the KD and modified Atkins diet in children and adolescents with refractory epilepsy, KD and its variations were considered as a promising treatment option in epilepsy, thanks to the beneficial clinical results regarding efficacy and safety.

Evidence in Adults

The benefits of the KD in the treatment of epilepsy in adults have not been clarified yet (28).
Martin-McGil *et al.* identified 13 studies with 932 participants; 711 children and 221 adults and concluded that the evidence suggests that KD demonstrate electiveness in children with drug-resistant epilepsy but that the evidence for its use in adults remains uncertain (29).
In a randomized control trial, the authors found a significant seizure reduction in the diet group compared to the controls, but only for moderate benefits (25-50% of seizure reduction) (28).
Husari *et al.* evaluated data from recent clinical trials showing that some adults with epilepsy achieve significant benefits with KD treatment stating that it is clear that some adults with epilepsy achieve significant benefits by the treatment with KD, but that future studies are needed to explore the effectiveness of this treatment in specific epilepsy syndrome (e.g. focal, generalized) (2).
Roehl *et al.* evaluated the efficacy of the modified KD on seizure frequency, severity and quality of life in adults with drug-resistant epilepsy; and observed a ≥ 50% seizure frequency improvement, 42 (76%) reported improvement in seizure severity, and 48 (87%) reported improvement in quality of life after 3 months of diet therapy (30).
Recent evidence suggests that KD treatments improve seizure control and improve other neurologic conditions, including nonmotor Parkinson's disease symptoms; specific themes that emerged from clinical trials in adults may impact and guide future studies (31).
A recent systematic review reports current evidence regarding the use of KD in adults, the results show that this therapy can be a good option, but the dates need to be interpreted with caution due to inherent bias and the small sample size of the studies included (32).
Another recent study in the United Kingdom investigated the effectiveness, retention, and safety profile of modified KD in adults with epilepsy and showed that modified KD can be effective in adults, although, even with regular dietetic support, retention rates remain low, and periods of worsening seizure frequency are common, nevertheless 60% of the patients improved seizure frequency, 38% experiencing > 50% of seizure reduction and 13% experiencing a seizure freedom (33).

CRITICAL ANALYSIS

We analyzed the beneficial effects of KD in epilepsy, but other aspects need to be considered before it can be called a 'miraculous diet' (8).
The most recurrent reported adverse effects related to KD treatment are gastrointestinal effects, weight loss, alteration in lipid profile (2), stress, constipation (30), vomiting (3), and all those often represent a reason to drop out the treatment. However, these side effects can generally be managed with extra dietary advice (e.g. increasing dietary fiber and fluid intake) (7).
Another important concern should be the diet compliance since several studies in adults shows compliances between 38 and 62.9%. Regarding compliance the modified Atkins diet seems a better option (2).
Mc Donald *et al.* evaluated whether the use of a ketogenic formula (KetoCal®) during the first month of modified Atkins diet can improve diet compliance in adults, and the results have shown that even though the supplementation does not increase the likelihood of reducing seizure it

significantly increases the compliance with the treatment (34).

KD, especially the more restrictive variants, are characterized by low variability, palatability, and tolerability; in recent years, to improve the quality of life in patients following the KD treatment, food companies have started to develop and commercialize, several food products for these patients like non caloric sweeteners, the use of 'ketogenic powders' and ketogenic liquid formulas', products rich in medium- or long-chain triglycerides. Other types of products that are growing on the market are ready-to-eat ketogenic products like biscuits, bread, focaccia, and desserts that improve the palatability and tolerability of the diet. Nowadays is possible to find 'ketogenic' 'foods as pasta, bread biscuits, and desserts with high protein content and low carbohydrates content (7).

A recent review (35) highlights other controversial questions which need to be discussed and researched in what regards to KD therapies; for example, maybe in the future KD may be used as a first-line treatment, or ketogenic treatment may be replicated in a pill or patients may be able to start the KD on their own without supervision. In addition, more research is needed about the potential adverse effects of KD therapy (e.g. bone health and menstrual cycle).

CONCLUSIONS

In conclusion, although there is a robust biologic plausibility and either mechanistic studies and randomized controlled trials supporting KD as a valid approach to reduce seizures in drug-resistant childhood epilepsy, the level of evidence is not as strong for the treatment of drug-resistant epilepsy in adults and many questions remain open due to study limitations, as low sample size, short-term follow-ups, the low compliance with the diet, and therefore, future studies are needed to clarify certain aspects of the relationship between KD and epilepsy management.

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