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Ketogenic diet in pediatric patients with epilepsy

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Abstract

Ketogenic diet (KD) is a version of low-carbohydrate diet, that is rich in fat, but also contains enough protein and very low carbohydrates supply. This diet may be one of the treatment option for children with refractory epilepsy and studies show that it reduces seizures. KD may affect behavioural and cognitive functioning in children and adolescents with refractory epilepsy. The main weakness of KD are possible adverse side effects included drowsiness, constipation, weight loss, vomiting, gastroesophageal reflux, fever, hyperlipidaemia and elevated risk of kidney stones development.

Keywords: ketogenic diet; pediatric; epilepsy

Introduction

Ketogenic diet is a type of low-carbohydrate diet, that is rich in fat, but also contains enough protein and very low carbohydrates supply. While being on that diet, intake of carbohydrates reduces to less than 50 g per day [1]. As a result, fat oxidation becomes the main source of power of human's body. It connects with appearance of so called ketosis, a state in which ketone bodies appear in blood in increased amounts.

The brain cannot produce energy from fat. After the organism run out of the glucose supplies, the alternative way of obtaining energy for it are ketone bodies produced during β -oxidation of fat acids: beta-hydroxybutyrate, acetoacetate and acetone. The process occurs mainly in hepatic mitochondria [2]. Human's brain fast gets used to using ketone bodies as energy. It starts acquiring energy from them after just four days. The full adaptation appears after around two weeks of ketosis [3].

Ketosis, which is a physiological state after periods without food containing carbohydrates, differs from diabetic ketoacidosis, which is pathological state. In the case of using the ketogenic diet, blood's pH does not change and ketone bodies do not exceed 8 mmol/l. However in diabetic ketoacidosis accompanying uncontrolled diabetes, ketone bodies appear in much higher amounts and blood's pH decreases [2].

Studies show, that low levels of glucose cause hypoglycemic reaction. Nevertheless, using low-carbohydrates diet for a long time causes production of big number of ketone bodies. After the test, in which participants were given a dose of insulin lowering their glucose level at the same time, the hypoglycemic reaction was only visible when they were not on low-carbohydrates diet. It proves that the body can work using ketone bodies as a source of energy [4].

As most of the calories during ketogenic diet comes from the fat, it is obvious, that they are a great part of the diet. Products rich in fat are for example: avocados, nuts, eggs, sunflower, olive oil, soy, fat cheese and meats, flax or fish. Food containing omega-3 acids have proven pro-health effects. We can mention beneficial effect in Alzheimer's disease, positive effect on fetus development, immune system, heart and vessels. During the diet, the biggest change is the smell from mouth. The reason is acetone, one of ketone bodies, which is eliminated mainly through the lungs [5].

Epilepsy is described as a group of neurological disorders which come with epileptic seizures, a visible symptoms of abnormal neurons' activity. They can have various forms- from short loss of consciousness to shaking, hypersalivation and even trismus. According to the definition, they have to be recurrent, unprovoked and separated by more than 24 hours. In reality though, it is hard to strictly keep to it.

Studies show, that incidence of epilepsy among children is different around the world. It varies between 35 to 128 per 100 000. Prevalence however stays around 3-11 per 1000 [6]. The cause of these disorders can be either related with genes or acquired. According to Dhiman et al. almost 50% cases have genetic basis [7]. Rest of them may occur after strokes,

tumors, head injuries, infections etc. Worth mentioning is also fact that about every fourth case among children is a refractory epilepsy. Treatment relies on many different drugs depending on the patient's characteristics, like valproate or lamotrigine [8].

Description of knowledge

Epilepsy may be well controlled with pharmacological antiepileptic treatment. However part of the patients suffer from epilepsy refractory to usual antiepileptic drugs. Therefore new possibilities of treatment are wanted. One of the new therapy options is ketogenic diet (KD) successfully used in refractory epilepsy treatment in children since the 1920s [9]. KD is an effective therapy option among children with refractory epilepsy but it is worth to highlight that medical supervision is needed [10]. Early introduction of seizures control and treatment is very important because it guarantees better development outcome among children [11].

Spanish scientists reviewed the data of 30 patients with refractory epilepsy who were on ketogenic diet. About one third of reviewed individuals had a positive response with reduction of their seizures for more than half an year. Nevertheless, possible adverse effects of ketogenic diet such as diarrhoea, vomiting, hypoglycaemia, constipation and weight gain should be taken into account. They could be prevented or treated without complications [12]. Also Cappola et al. observed the significant reduction of seizures among children aged between 3 months and 5 years, affected by symptomatic partial epilepsy and cryptogenic-symptomatic epileptic encephalopathies. Adverse side effects including drowsiness, constipation, weight loss, vomiting, gastroesophageal reflux, fever, and hyperlipidaemia were present in 65.8% cases [13]. Neal and his team came to similar conclusion. In their study 145 children aged between 2 and 16 years were enrolled and randomized to study group receiving ketogenic diet or control group. After 3 months the number of seizures in study group was significantly lower in comparison to control group [9]. In other study Neal et al. examined which of the KD option: classical or medium-chain triglyceride ketogenic diet is characterized by better efficacy. They assessed seizure frequency after 3, 6 and 12 months of KD diet initiation among children with intractable epilepsy. Both options of KD were comparable in efficacy and tolerability [14].

Evangelidou et al. examined the role of the branched chain amino acids as adjuvant therapy to the KD among children with refractory epilepsy. The study shows that addition of branched chain amino acids reduced the number of seizure in patients with epilepsy. The findings indicate that branched amino acids could improve effectiveness of KD. The limitation of this study was the fact that experimental group was small (17 children) [15]. KD may affect behavioural and cognitive functioning in children and adolescents with refractory epilepsy. Ijff et al. conducted study in which 50 patients with epilepsy were included and divided into the study group or control group. 4 months after ketogenic diet initiation follow-up assessments on cognition and behaviour were performed. In this study also parent report survey and individually administered psychological tests were conducted. Scientists observed a positive influence of the KD on behavioural and cognitive functioning [16].

Ketogenic diet besides advantages has a few disadvantages. KD may contribute to nutritional deficiency e.g. micronutrient status. Christodoulides et al. observed changes in plasma vitamins A and E and the decline in magnesium status after one year of ketogenic diet treatment among children [17]. Another negative aspect is the fact that classic ketogenic diet could affect serum lipid profile. Zamani et al. assessed serum lipid profile of children with refractory epilepsy being on ketogenic diet. The serum lipid profile was measured 3 and 6 months after KD initiation. Median triglyceride, median total cholesterol, median serum low-density lipoprotein (LDL) and median serum high-density lipoprotein (HDL) were significantly increased [18]. Similar observation was described in study conducted by

Nizamuddin et al. Additionally they find that children receiving a solely formula-based ketogenic diet had lower cholesterol level than those eating solid food after adjusting for age and initial ketogenic ratio [19]. Sampath et al. performed cohort study in which children (n=195) started ketogenic diet (from 2000 to 2005) were included. They observed kidney stones presence in this group. About 1 in 20 children developed kidney stones. They find also that, oral potassium citrate supplementation significantly decreased the prevalence of stones (3.2% vs 10.0%, $P = .049$) [20].

De Kinderen et al. studied the cost effectiveness of KD among children and adolescents with most difficult epilepsy compared to usual care. The study group included 48 individuals, aged 1-18 and randomized into KD group or control group. Although the seizure frequency in KD group was reduced, there was no improvement in quality of life. The mean per patient costs in control group were lower in comparison to KD group (15,245€ vs. 20,986€) [21-22].

Conclusion

The ketogenic diet is characterised by high-fat and low carbohydrate composition which may be one of the treatment option for children with refractory epilepsy. The fact that ketogenic diet reduces the number or severity of seizures is confirmed. Additionally ketogenic diet has positive effect on behaviour. The main weakness of KD are possible adverse side effects included drowsiness, constipation, weight loss, vomiting, gastroesophageal reflux, fever, hyperlipidaemia and elevated risk of kidney stones development and high costs. However they may be prevented or treated without complications.

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