Dietary therapies for childhood epilepsy

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Summary

Ketogenic diet composed of high fat and low carbohydrate was introduced as a therapeutic alternative for epilepsy in early 20's. As new antiepileptic agents such as phenytoin were discovered, the popularity of the diet waned until 90's. Studies on efficacy of diet in refractory epilepsy reported that approximately half of the children had a significant reduction 15% of whom were seizure free. With growing body of evidence and introduction of diet modifications, ketogenic diet was promoted as a first line treatment for epileptic encephalopathies such as myoclonic-astatic epilepsy, Dravet syndrome and infantile spasm. (Turk Arch Ped 2013; 48: 275-280)

Key words: Dravet syndrome, epilepsy, infantile spasm, ketogenic diet, myoclonic astatic epilepsy

Introduction

Currently, seizures of most epilepsy patients can be controlled with anticonvulsant drug treatment, while resistant seizures of some patients direct physicians to search for other treatment methods. The relation of this kind of resistant epilepsies with nutrition has been known for long years. In the beginning of the 1900’s, investigators drew attention to the fact that epileptic seizures could be stopped by complete fasting (1,2). However, naturally complete fasting is not a sustainable treatment method. Therefore, a diet which mimicked acidosis, fluid loss and ketosis which occur in the fasting state and which could be used for years was developed by Dr. Wilder (3) in 1921 in Mayo Clinic. This treatment which is called ketogenic diet (CD) has been used in treatment of epilepsy for more than 100 years without a change in its content. With release of phenytoin in 1938 drug therapies came to the forefront and use of CD decreased in the following years. In the second half of the 20th century, a few centers in which diet therapy was being used remained and most neurologists regarded diet therapies as “alternative” or “complementary” medicine. However, initiation of CD in 1994 in a 2 year-old epileptic boy in whom multiple drugs and surgical treatment were unsuccessful with the intervention of the family and improvement of seizures completely (4) once again increased the attention of physicians and families related with diet therapies. In the last 20 years, hundreds of publications have been added to the medical literature, international symposiums have been arranged and consensus reports have been published (5,6). In this article, ketogenic diet and other diet methods in treatment of childhood epilepsies will be discussed because of their current significance.

What is ketogenic diet?

Ketogenic diet is a nutritional regime containing high fat, low protein and low carbohydrate and its calorie and total fluid content is limited to meet 80% of daily requirement. The ketogenic ratio (KR) is calculated as the ratio of fat contained in the diet to the sum of protein and carbohydrate and it is 4:1 for a typical CD (5). A higher ketogenic ratio means more ketosis. In patients in whom protein requirement is high or diet cannot be applied...
appropriately because of side effects including infants and adolescents, lower ratios including 3:1 or 2:1 can be used (7). In a diet with a ketogenic ratio of 4:1, 90% of the daily calorie is provided by fat, 7% is provided by protein and 3% is provided by carbohydrates (8). The most common sources of fat include butter, cream, oil and mayonnaise.

Ketogenic diet lists should be prepared individually for each patient. Keeping a three-day diet record of the patient is recommended in terms of determining food preferences and preparing a diet list compatible with the palatal delight. The aim should be to give enough calorie such as to follow up the patient’s own growth curve while arranging nutrition. Fluid restriction during ketogenic diet is controversial. Since a marked efficiency of fluid restriction has not been demonstrated in stopping seizure activity, it is no longer used in most centers (8,9). Since it is observed that most epilepsy patients receive not even 80% of daily fluid requirement before CD when diet records are kept, the term limitation is not accurate (10). It is recommended that 100% of daily fluid should be given to patients who are immobile, who have a history of nephrolithiasis and who use carbonic anhydrase inhibitor (topiramate, asetazolamide, zonisamide) (11).

In the begining of the treatment method, it is recommended that patients should be followed up by hospitalization, because patients will enter a 24-48-hour fasting period in the beginning of CD. During the fasting period, blood glucose levels should be measured every 4-6 hours and urinary ketone should be tested daily (8). At the time of hospitalization and in the following days, serum electrolytes, urea, creatinine should be measured daily. The patient should be weighed every morning and his/her input/output fluid should be recorded. The diet should be arranged such as to complete urinary ketone at the moderate-high level (80-160 mg/dL) (9). Nutrition is opened gradually in three days following fasting, the highest level is reached and the patient can be discharged. The problems which can be encountered during the fasting period include transient hypoglycemia, vomiting, constipation and mild acidosis and these conditions can be easily intervened in the hospital setting. Some authors have reported that equal efficiency occurs in seizure control without fasting period, but fasting is still applied in most centers, since it is thought the effect starts faster with fasting (12).

Ketogenic diet is a type of diet which has an unpleasent taste because of its high fat content and which can be compensated with difficulty (6). Therefore, other diet therapies which are more appropriate for palatal delight and which have a higher carbohydrate and protein content compared to CD have been developed. Currently, there are three more diet therapies other than classical CD which have been proved to be efficient in treatment of epilepsy and which are being used: medium chain triglyceride (MCT) diet, modified Atkins diet (MAD) and low glycemic index therapy (LGIT). In these therapies, the protein and calorie rates received by patients are higher, they can be compensated better and limit weight gain and growth with a lower rate (Table 1). In addition, the patient does no need to be hospitalized to initiate the diet, since fasting is not required in advance (13,14).

Since medium chain fatty acids produce more ketone per unit energy (15), patients who use MCT diet can consume less fat and more protein and carbonhydrate compared to CD. Thus, food options become richer. However, compliance is low, since foods should be weighed and measured and time should be spent during preparation of meals (16). In low glycemic index therapy, only foods with a glycemic index below 50 are allowed. Although this type of diet contains a richer food spectrum and more protein, approximately 1/4 of patients have found this diet excessively limiting (17).

In MAD which was started to be used by Kossoff and his team in 2003 in Johns Hopkins Institute for the first time, there is no calorie, fluid or protein limitation (13). In this diet, carbohydrates are limited up to 10 g/day and high fat intake is supported to provide ketosis. In MAD which is

| Table 1. Comparison of four different diet types for nutrition containing 1500 kcal daily |
|--------------------------------------|--------|--------|----------------|
| Diet                                 | Fat (g), % calorie | Protein (g), % calorie | Carbohydrate (g), % calorie |
| Classical ketogenic diet              | 150 (%90) | 25.5 (%7) | 12 (%3) |
| 4:1                                  | 144 (%)   | 27 (%)  | 21 (%)  |
| 3:1                                  | 138 (%)   | 30 (%)  | 39 (%)  |
| 2:1                                  | 115 (%)   | 55 (%)  | 60 (%)  |
| 1:1                                  | 117 (%)   | 37.5 (%10) | 75 (%20) |
| OMedium chain triglyceride diet      | 100 (%60) | 100 (%27) | 50 (40-60) (%13) |
| Low glycemic index therapy           | 117 (%70) | 94 (%25) | 19 (%5) |

*Values are calculated approximately.*
preferred by many centers currently, ketone production is variable and its efficiency has been shown to be increased with supportive high-fat formulas in the first month of treatment (18). It is recommended that the diet most appropriate for the patient’s compliance should be selected in accordance with the patient’s individual properties and the views of families and dietician, because it is impossible to continue the efficiency of treatment if close monitoring is not provided (16).

The place of ketogenic diet in treatment of epilepsy

It has been reported that ketogenic diet may be useful in many seizure types and resistant epilepsy. The limits of diet indications which were previously defined for cases unresponsive to at least two anticonvulsant drugs with frequent seizures and not appropriate for epilepsy surgery become more clear with the study of the International Ketogenic Diet group published in 2009 (5). Two special conditions in which ketogenic diet can be used as the first-line therapy have been defined: Glucose transporter type 1 deficiency and piruvate dehydrogenase deficiency. In glucose transporter type 1 deficiency, glucose transportation in the blood-brain barrier is disrupted; microcephaly, resistant seizures and movement disorders occur in the patients (19). In piruvate kinase deficiency, piruvate cannot be transformed to acetyl-coenzymze A and a neurodegenerative picture accompanied by seizures occurs (20). With ketogenic diet ketone (acetoacetate, beta hydroxy butirate) is provided to the brain as optional fuel instead of these metabolic pathways.

Recent reports about the efficiency of MAD and LGIT which can be applied more easily compared to classical CD in epileptic patients suggest that diet therapy can be applied earlier in epilepsy (13,14). Considering the extensiveness and ease of use of ketogenic formula, it is expected that diet treatment will be used extensively in infants with infantile spasm in the forthcoming period. Hong et al. (21) reported that the seizure frequency decreased by more than 50% in 64% of 1104 patients with infantile spasm in a diet period of 6 months and 34% of the patients remained seizure-free in the study they published in 2010. The authors emphasized that diet treatment could be considered just after failure of adrenocorticotropic hormone and vigabatrin treatment.

It has been reported that ketogenic diet is superior to new anticonvulsant drugs in patients with myoclonic astatic epilepsy which is one of the myoclonic epilepsies of genetic origin (22). In patients with Dravet syndrome which is another form of this epilepsy group, Nabbout et al. (23) found that diet decreased attention deficit in 56% and impulsivity and nervousness in 28% in addition to seizure control. Although especially vigabatrin has been shown to be effective in seizures related with tuberosclerosis, different centers have reported that ketogenic diet might be an efficient alternative method together with surgical treatment even in focal seizures (24,25).

Conditions for which the efficiency of diet is being reported are increasing gradually in the form of case reports or series. The efficiency of diet has been reported in seizures related with Rett syndrome, Lafora body disease, Landau Kleffner syndrome which is known as epileptic aphasis and neuronal seroid lipofuscinosis which is a lysosomal storage disease (26). Fever induced refractory epileptic encephalopathy (FIRES) is a picture of encephalopathy described in previously healthy children. In these patients, no specific infectious agent can be found and a refractory status picture is typical. Probably, the most amazing results about classical ketogenic diet included small case series in which status epilepticus was reported to be terminated in these patients (27,28).

The mechanism of action of ketogenic diet

Investigators usually have to develop methods in the opposite direction to elucidate the mechanism of action of ketogenic diet; understanding the reason of a method which is known to be effective instead of searching for treatment for a disease of which the pathophysiology is known. Increasing investigations indicate multiple variables working synergistically instead of a single mechanism of action (29).

In early animal studies, the convulsion-preventing effects of administration of inpraperitoneal acetocetate had been shown in different experimental models (30,31). In Mouse models of Dravet syndrome, a relation was found between high beta-hydroxybutirate levels and seizure control (32). In addition to investigators (33) who have reported that ketogenic diet with a higher ketogenic ratio (6:1) are more efficient, there are many studies in which seizure triggering has been shown to be prevented after ketosis (34,35,36). With ketogenic diet the number and affinity of GAMA receptors increase and the synthesis of endogenous glutamate antagonists is induced (37,38). Studies based on the assumption that multiple unsaturated fatty acids can equilibrate neuronal cell have yielded contradictory results (39,40). Ketogenic diet has been shown to protect hippocampal cells from glutamate-mediated excitation damage and its neuroinflammatory protector property has been emphasized (41). Ketones protect the brain from free oxygen damage by decreasing cerebral coenzymze Q10 semiquinone levels and stimulating hippocampal glutation peroxidase (42,43). In addition, it has been shown that diet increases neuronal high-energy molecular densities (44).

Recently, the effect of ketogenic diet on carbohydrate metabolism and leptin levels has drawn the attention of investigators. High fat intake and limited carbohydrate inhibit the glycolysis pathway. Glucose analog 2-deoxy
D-glucose which inhibits the glycolysis pathway show marked anticonvulsive effect acutely and chronically (45). Acute action has been associated with inhibition of postsynaptic currents and chronic action has been associated with regulation of the brain-derived neurotrophic factor (BDNF) gene (46,47). It is thought that increased leptin levels with diet are involved in the effect of anticonvulsive effect of ketogenic diet. Increased leptin levels decrease the frequency and time of seizures by inhibiting AMPA-related excitation (48).

**Contraindications of ketogenic diet**

In some metabolic diseases, application of CD is contraindicated; these include pyruvate carboxylase deficiency, primary carnitine deficiency, fatty acid oxidation disorders (including carnitine transporter disorders) and porphyria (16). Therefore, patients with refractory epilepsy selected for CD should be screened in terms of these diseases before diet (Table 2).

Relative contraindications include nephrolithiasis, hypercholesterolemia, combined use with phenobarbital and severe gastroesophageal reflux (8,16)

**Side effects of ketogenic diet**

Independent of the diet type, CD treatment is a significant therapy method with potential side effects (49). Therefore, families should be informed about the fact that CD is not a “natural” or “complementary” treatment method before starting this diet.

In addition to transient side effects observed in the fasting period, renal stones, dislipidemia and pause in growth may be observed in 5% of the patients (50,51,52). None of these side effects necessitate discontinuation of treatment. However, intolerance related with gastrointestinal side effects (vomiting, loss of appetite, constipation, fecal) and discontinuation of diet is observed especially in adults (53). Since albumin and carnitine levels of the patients may decrease, measurement of blood levels is useful. Although carnitine support is controversial, it is recommended only in patients who feel weak despite intake of sufficient calorie (54). Specific vitamin deficiency or mineral deficiency including selenium and progressive loss of bone mineral compound may be observed (55). Very rarely, cases of cardiomyopathy related with association of acidosis and selenium deficiency (56) and fatal pancreatitis related with hyperlipidemia (57) have been reported.

**Follow-up and prevention of complications**

Patients who receive ketogenic diet should be followed up in special centers by a team composed of physicians and dieticians. One mission of the ketogenic diet team is to prevent complications before they develop. Alternative diet therapies including modified Atkins diet or LGID or starting diet without fasting may be considered (12).

Before discharge from the hospital, families should have received diet education and learned to measure urinary ketone. In most centers, calcium, vitamin D, zinc and selenium supplements are prescribed to patients before discharge (58). Afterwards, evaluation of growth, nutrition and activity is recommended with 3-month intervals by outpatient follow-up (Table 2). At each clinical visit, fasting lipid levels, complete blood count and detailed metabolic examination should be ordered (5). Urinary calcium/creatinine ratio should be evaluated and oral alkalinization should be performed in patients with a high urinary calcium/creatinine ratio. Administration of oral citrate empirically with this objective (2 mEq/kg/day, in two doses) has been shown to decrease the frequency of nephrolithiasis from 6.9% to 0.9% (59). In patients with severe hyperlipidemia, KR may be reduced or switching to multiple unsaturated fatty acids may be applied (10). Cardiac evaluation by yearly echocardiogram should be kept in mind (16). If ketogenic diet does not provide seizure control, diet is generally recommended to be discontinued after 3-6 months. In patients in whom diet is efficient, no decrease in seizure control has been reported when diet is discontinued after two years. However, diet therapy can be continued for a long time in children showing a normal growth-development in whom anticonvulsant drugs can be discontinued (10).

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**Table 2. Tests to be ordered and follow-up chart in ketogenic diet**

<table>
<thead>
<tr>
<th>Before starting</th>
<th>Definition of daily calorie requirement according to age, height, body weight and level of mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Fasting lipid profile, urea, creatinine and electrolytes, urgent carnitine, lactate</td>
</tr>
<tr>
<td>Urine</td>
<td>Measurement of pH and density, Ca/Cr ratio, organic acid</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Evaluation of growth by measurement of height, weight</td>
</tr>
<tr>
<td>Physical examination (every three months)</td>
<td>Complete blood count, calcium, phosphorous, magnesium, alkaline phosphatase, fasting lipid profile, albumin, lipase, hepatic transaminases, anticonvulsant drug levels, 25-hydroxy vitamin D, carnitine, beta-hydroxy butirate</td>
</tr>
<tr>
<td>Urine</td>
<td>Complete urinalysis, Ca/Cr ratio</td>
</tr>
<tr>
<td>Cardiological evaluation (yearly)</td>
<td>Echocardiogram</td>
</tr>
</tbody>
</table>
Conclusion

Ketogenic diet therapy is a convenient treatment option with confirmed efficacy in resistant childhood epilepsies. Currently, ketogenic diet has been included in the first-line therapies in selected patients. In our country, the number of centers where ketogenic diet is applied will increase as the awareness of physicians about ketogenic diet increases.

References