

## Dietary therapy for epilepsy

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### CLINICAL REVIEW

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**Children with pharmacoresistant epilepsy should be offered ketogenic dietary therapy. The diet, which is rich in fat and low in carbohydrate, has a beneficial effect in reducing seizures in this patient group. It may also have a beneficial effect in adults, but there is less evidence than in children. Dietary treatment of epilepsy is a specialist therapy, and in order to adhere to the diet, strong motivation of the patient and relatives as well as close follow-up from the specialist health service are necessary.**

Active epilepsy has a prevalence of approximately 0.7 %, equivalent to 37 000 people in Norway (1). Of these, two-thirds achieve good control of their seizures with the aid of antiepileptic drugs (2). Of the approximately 12

000 people with pharmacoresistant epilepsy, i.e. those who suffer from recurring seizures despite having tried two of the most relevant antiepileptic drugs in adequate doses over a sufficiently long period, some may be helped by epilepsy surgery or vagus nerve stimulators, and some may benefit greatly from dietary therapy.

Ever since the time of Hippocrates it has been known that fasting may have a beneficial effect on epilepsy. Trials of fasting in the early 1900s confirmed this. In 1921, Wilder at the Mayo Clinic in the USA suggested that the seizure-reducing effect of fasting was caused by ketosis. He developed a ketogenic diet that mimics the body's metabolism when fasting (3). Although solid documentation of the seizure-reducing effect of this diet was produced over the subsequent 20 years (4), the interest in such therapy declined after the introduction of phenytoin in 1938.

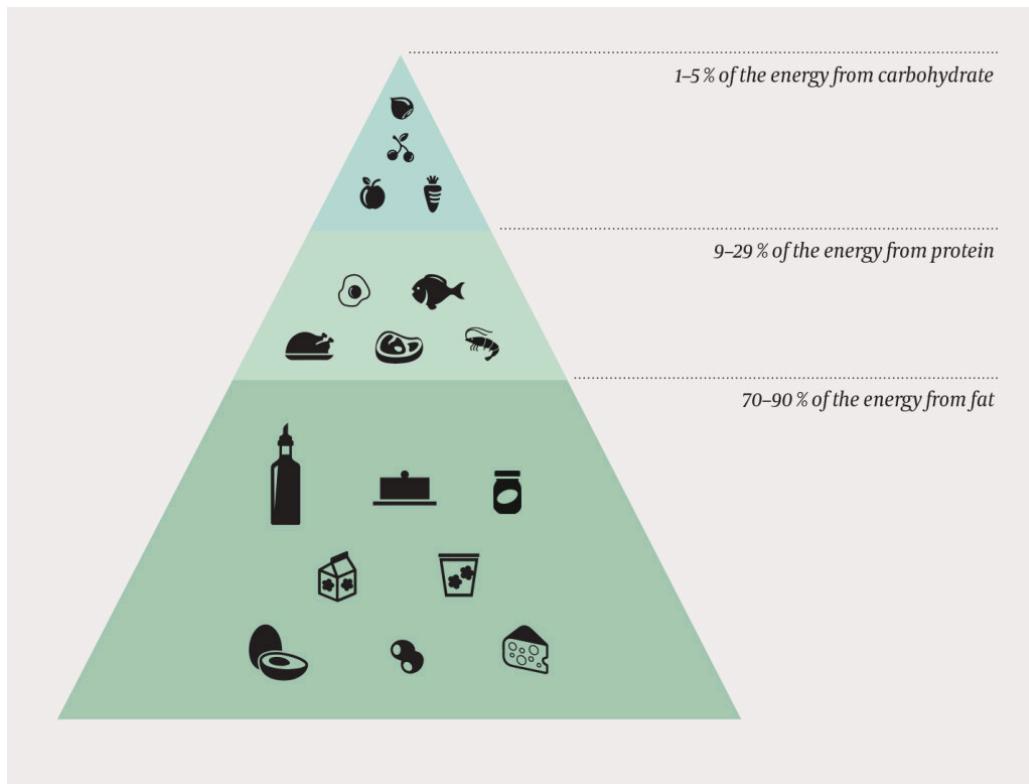
Over the last 20 years, this diet has undergone a renaissance and is now in use all over the world, mainly in children (4). At the National Centre for Epilepsy in Norway, the ketogenic diet has been an option for children since the 1990s. Since 2010, this therapy has also been offered to adult patients.

In this article we provide a brief overview of the current state of knowledge regarding dietary therapy for epilepsy, based on searches in PubMed and our own clinical experience. We also provide advice on the types of patients for whom this therapy will be best suited.

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## What is a ketogenic diet?

A ketogenic diet is a collective designation for a number of diets that include a lot of fat, adequate amounts of protein and very little carbohydrate (4) (Figure 1). The body's metabolism changes from glycolysis to beta-oxidation. The term **ketogenic ratio**, i.e. the ratio between grams of fat and grams of protein plus grams of carbohydrate, is used.



**Figure 1** The ketogenic diet pyramid shows the main groups of foods used in a ketogenic diet as practised at the National Centre for Epilepsy. Fatty foods account for most of the energy. There is a moderate amount of protein-rich foods, and carbohydrates account for a very modest proportion of the energy intake. There are various types of ketogenic diets, and the amounts from the different food groups vary between them.

The classic ketogenic diet is strict and may be hard to maintain. In 1971, the MCT (medium chain triglycerides) diet was introduced, a modification of the ketogenic diet with medium-chain fatty acids. MCT produce a higher ketosis than long-chain fatty acids, but may cause gastrointestinal symptoms. MCT may also be used as a supplement to other diet variants (4).

In recent years, less rigid diet variants have been introduced, such as the modified ketogenic diet (the modified Atkins diet) and the low glycaemic index diet (4, 5) (Box 1).

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**Box 1. Brief overview of ketogenic diet variants and their use in cases of pharmacoresistant epilepsy (4)**

**Classic ketogenic diet**

Ketogenic ratio 2:1 – 4:1, adequate amounts of protein. Up to 90 % of the energy comes from fat. Meals are carefully calculated and composed to provide the same amount of energy, fat, protein and carbohydrate in each meal.

Ingredients are weighed with an accuracy of 0.1 grams. The same number of meals are taken every day and at the same times. Used in children with pharmacoresistant epilepsy and patients with gastrostomy.

**MCT diet**

Similar to the classic ketogenic diet, but 30 – 60 % of the fat is replaced by MCT oil. More carbohydrates are included than in the classic ketogenic diet, and the

diet may include a larger variety of foods. MCT oil may cause gastrointestinal symptoms.

### **Modified ketogenic (Atkins) diet**

The amount of carbohydrate is limited to 10 – 30 grams per day. Aside from this rule, the patient may decide meal frequency and amounts, which may vary from one day to another. A high intake of fat is encouraged. Used for older children, adolescents and adults.

### **Low glycaemic index diet**

The intake of carbohydrate is limited to 40 – 60 grams per day, including fibres, and the carbohydrate must have a glycaemic index of < 50 (5). There is little documentation available on the effect of this diet on pharmacoresistant epilepsy, and it is not widely used in Norway.

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## **What is eaten?**

Fatty foods such as vegetable oils, margarine, mayonnaise, avocado, nuts, seeds, olives and full-fat dairy products account for a considerable proportion of the diet (4). The diets contain moderate amounts of protein-rich foods, such as pure meat and fish, eggs and cheese, cf. Figure 1. Sources of carbohydrate include vegetables, fruit, berries, dairy products and nuts. Carbohydrate-rich staples such as bread, potatoes, rice and pasta are not suitable for a ketogenic diet, but there are good recipes for ketogenic variants of crispbread, pasta, waffles, cakes and desserts.

## **Mechanisms of action**

During the therapy, the body's metabolism changes. Blood sugar levels decrease, and the body starts burning fat as its main energy source. When fat is broken down, ketones (acetate, acetoacetate and betahydroxybutyrate) are formed, and these are used by the brain as an energy source instead of glucose.

The underlying cause of the anti-seizure effect of this diet is not understood, but many hypotheses have been postulated, including increased mitochondrial biosynthesis, reduced glycolysis, increased GABAergic inhibition, reduction in oxidative stress, anti-seizure effect of ketone bodies, increased leptin concentrations and influence of polyunsaturated fatty acids on sodium, potassium and calcium channels (6). Most likely, the effect is produced by multiple synergistic mechanisms.

## **Practical implementation**

At the National Centre for Epilepsy, we initiate the classic ketogenic diet in children upon admission, while the modified ketogenic diet normally starts at home. Training in meal recipes and calculation of the food composition is

provided by a clinical nutritionist. For tube feeding, medical nutritional products or pureed foods are used (4).

We have observed that some patients experience discomfort caused by hypoglycaemia and transient high ketosis during their first weeks on the diet. There is a risk of metabolic acidosis. Normally, we observe that blood sugar levels and the HbA1c value stabilise in the lower section of the reference area. Ketones can be measured in blood and urine after a few days – 'the patient is in ketosis'. During the first weeks, the caloric content or the fat and carbohydrate intake are adjusted for an optimal effect. This is always a topic in later follow-up, in the outpatient clinic or during admission.

There is international consensus that the treatment in children should be attempted for three months before its efficacy is assessed (7). If the effect is beneficial, the treatment can continue for many years. At the National Centre for Epilepsy we monitor children every 3 – 6 months, while adults are monitored annually.

Most patients continue taking antiepileptic drugs after starting the diet, but we find that some may reduce the number of drugs or the dosage. We have observed clinically relevant declines in the serum concentration of antiepileptic drugs after introducing the diet (8). The cause of this decline is unknown.

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## Which patients should be provided with this option?

The ketogenic diet is a treatment option for patients of all ages with pharmacoresistant epilepsy (7, 9, 10). Although the evidence to date of its effect is far stronger for children than for adults, our experience and that of others indicates that dietary therapy should also be considered in therapy-resistant adult patients.

For a long time, many regarded the diet as a 'last resort', but 81 % of the members of an international consensus group agreed that the diet should be attempted in children in whom two drugs had been tried without satisfactory effect, and where epilepsy surgery was not an option (7). In our opinion, dietary therapy should be considered in both children and adults who have not achieved control of their seizures after trying two relevant antiepileptic drugs and who do not want epilepsy surgery or for whom this is not an option.

The diet may be effective in focal as well as generalised forms of epilepsy (7, 9, 11). It may have an anti-seizure effect for a number of paediatric epilepsy syndromes, such as West syndrome, Dravet syndrome, Rett syndrome, Lennox-Gastaut syndrome, tuberous sclerosis and syndromes associated with defects in the respiratory chain (7).

The ketogenic diet is the first-line choice in certain rare metabolic encephalopathies such as glucose transport protein type 1 deficiency and pyruvate dehydrogenase deficiency, chiefly as a metabolic treatment of the underlying disorder (7). The diet has been attempted in adults and children with super-refractory status epilepticus, but the results are uncertain (9, 12).

In children under two years, such diets are used with caution because of the risk of malnutrition. On condition that close follow-up be provided by an interdisciplinary team, we believe that it will be relevant to attempt dietary therapy for this group as well – because it will often have a good effect in children (13).

Certain rare conditions are *not* amenable to dietary therapy. Examples include defects in fatty acid oxidation, primary carnitine deficiency, organic aciduria and pyruvate carboxylase deficiency. The ketogenic diet is also advised against in cases of familial hyperlipidaemias, unexplained hypoglycaemia, severe gastroesophageal reflux, severe liver disease and diseases that require a high intake of carbohydrate, such as porphyria (7). In patients with insulin-dependent diabetes, certain mitochondrial diseases and when steroids are used, the diet is also less suitable.

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## Anti-seizure effect

Most clinical studies of the ketogenic diet have been undertaken in children with pharmacoresistant epilepsy. Summarised data from non-controlled studies show that 33 – 56 % of the children achieve a > 50 % reduction in seizures and 16 % become totally seizure-free (4).

A recently published Cochrane study concluded that at least 38 % of the children achieved a > 50 % reduction in seizures (14). Three randomised, controlled studies have been conducted of children with pharmacoresistant epilepsy, in which dietary therapy was compared to drug-based treatment. The effect was assessed after three or four months. Neal and collaborators randomised 73 children to a ketogenic diet and 72 children to continued drug-based treatment, and found that 38 % of the dieting children had > 50 % reduction in seizures, compared to 6 % in the control group ( $p < 0.0001$ ). Altogether 7 % of the dieting children achieved > 90 % reduction in seizures, compared to none in the control group (15). The English group also compared the classic ketogenic diet with the MCT diet and found the same effect for the two diet variants (16).

An Indian research group randomised 50 children to a modified Atkins diet and 52 children to continued drug-based treatment. Fully 30 % of the dieting children achieved > 90 % reduction in seizures, against 7.7 % in the control group ( $p = 0.005$ ). Altogether 52 % of the children in the dieting group achieved > 50 % reduction in seizures, against 11.5 % in the control group ( $p < 0.001$ ) (17).

In a Dutch study, altogether 50 % (13 of 26) of the participants in the dieting group achieved a reduction in seizures of more than 50 %, compared to 18.2 % in the control group (18).

A Scandinavian review of 290 children using a ketogenic diet in 1999 – 2009 showed that 50 % of the children achieved at least a 50 % reduction in seizures after six months and 16 % were totally seizure-free (19).

Prospective small-scale studies of dietary therapy in adults with pharmacoresistant epilepsy have shown a weaker effect than in children. A review article from 2014 states that approximately 30 % of the patients achieved > 50 % reduction in seizures, and that 9 % of these achieved > 90 % reduction (9).

In children who continue their dietary therapy over a number of years, it seems that the seizure-reducing effect is maintained for as long as the therapy continues (20), and those who have remained seizure-free for two years with the aid of the diet may gradually revert to a normal diet without seizures recurring (21). We are not aware of any publications that describe long-term results for adults.

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## Other beneficial effects

In addition to fewer seizures, Hallböök and collaborators have reported shorter and weaker seizures, improved sleep quality, attention and quality of life among children on a ketogenic diet (22). Ijff and collaborators found that the diet has positive effects on the cognitive functions of children and adolescents (23). This is consistent with our own experience from work with children and adults.

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## Unwanted effects

Constipation, vomiting, diarrhoea, weight loss, reduced energy and hunger are the most common adverse effects reported in children during the first three months on a classic or modified ketogenic diet (14, 15). With close follow-up and adjustments to the diet, these adverse effects are soon eliminated or reduced.

Our experience indicates that most adults tolerate a modified ketogenic diet (Atkins) well, but that weight loss, constipation and a slight increase in cholesterol level are fairly common. This is corroborated by the literature (9).

Rare cases of pneumonia, sepsis, acute pancreatitis, gallstones, kidney stones, status epilepticus, acidosis, fatty liver, dehydration, abdominal pain, tachycardia and hyperammonaemic encephalopathy have been reported (14).

There is little knowledge about unwanted long-term effects in both children and adults. The increased incidence of kidney stones may partly be explained by the previous practice of restricting fluids as part of the therapy (7).

Preventive treatment with calcium citrate is provided as needed (7, 15, 19). In children, a ketogenic diet may cause growth retardation (20), and bone demineralisation has been reported (4). Some of our patients report an increased number of bruises. Disruptions of the menstrual cycle also occur (24).

A study of pseudo-markers of vascular disease in children (cholesterol levels, carotid intima-media thickness and elasticity) showed a deterioration in such markers, but the findings are conflicting (25, 26). Because cholesterol levels increase in some patients, we recommend reducing saturated fat in favour of mono- or polyunsaturated fat. We are not aware of any reports of cardio- or cerebrovascular events associated with atherosclerosis as a result of long-term ketogenic dietary therapy.

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## High attrition rate

The diet may be challenging. Among children on a classic ketogenic diet we have observed very low attrition rates, but the literature reports 4.2 – 20.8 % attrition, and for the modified ketogenic diet (Atkins), the attrition rate is 8 – 50 % (14). Many adults refrain from trying or discontinue early (9). In our experience, the success and retention rates depend on well informed and motivated patients and next of kin, as well as on close follow-up by a highly skilled team from the specialist health service.

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## Referral routines

In Norway, the National Centre for Epilepsy fulfils a nationwide function for ketogenic dietary therapy in patients with pharmacoresistant epilepsy. The centre has a diet team consisting of a paediatric neurologist/neurologist, a clinical nutritionist and nurses. Patients with pharmacoresistant epilepsy who have been assessed by the specialist health service may be referred to the centre for assessment of dietary therapy.

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