Ketone monitor for ketogenic diet in epilepsy

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Recent review date: 4/2021

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Policy contains: Ketone monitoring device; ketogenic diet in epilepsy.

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Coverage policy

Ketone monitoring devices for members with epilepsy prescribed ketogenic diets are investigational/not clinically proven, and therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Urine test kits to test for ketones in members on the ketogenic diet for epilepsy.

Background

About 5.1 million Americans have a history of epilepsy, and 2.9 million have active epilepsy (Centers for Disease Control and Prevention, 2020). The ketogenic diet is a special high-fat, low-carbohydrate diet in us since the 1920s (Rogovik, 2010) that helps to control seizures in some people with epilepsy. It is prescribed by a physician and carefully monitored by a dietitian. It is stricter with calorie, fluid, and protein measurement and occasional restriction than the modified Atkins diet, which is also used today. The diet is a potential option for treating epilepsy, as 1/3 of people with the disease are resistant to medication (Dhamija, 2013).

Ketogenic means a producer of ketones in the body (keto = ketone, genic = producing). Ketones are organic compounds formed when the body uses fat for its source of energy. Usually the body uses carbohydrates (such as sugar, bread, and pasta) for its fuel, but because the ketogenic diet is very low in carbohydrates, fats

become the primary fuel instead. Ketones are not dangerous. They can be detected in the urine, blood, and breath. Ketones are one of the more likely mechanisms of action of the diet, with higher ketone levels often leading to improved seizure control. However, there are many other theories for why the diet will work. There are probably multiple mechanisms by which the ketogenic diet suppresses seizures (Bough, 2007).

The traditional ketogenic diet entails an initial fasting and dehydration period, during which patients receive no food, and fluid intake is limited until ketones are present in the urine. Thereafter, a diet high in fat and low in carbohydrates and protein is introduced. Strict compliance with this unpalatable dietary regimen has been shown to have anticonvulsant effects, particularly in children. Hospitalization may be necessary during an initial starvation period to induce marked ketosis and weight loss. The length of hospital stay depends on the proposed initial starvation period and generally should not exceed three days.

Results of studies of ketogenic diet are believed to have a broad spectrum of effects that may be beneficial in the treatment of different types of epilepsy and associated comorbidities such as cognition impairment, psychiatric disturbance, and sudden unexplained death (Meira, 2019).

The ketogenic diet is just one means of treating epilepsy that is not responsive to medications. Another, more recent method is low glycemic index treatment, designed to simplify the implementation of the ketogenic diet (Rezaei, 2018). Another is the modified Atkins diet, introduced in 1970 (Meira, 2019).

Ketone monitoring is performed by measuring serum and/or urine levels to assess if any medical problems exist (McNally, 2012). Urine testing, the most commonly-used technique, measures ketoacetate levels, while blood testing measures beta-hydroxybutyric acid (Martins, 2019). In children with epilepsy on a ketone diet, monitoring is performed by physicians every 1 – 3 months. In addition, height and weight are measured in case the child's growth is slowed (Kossoff, 2017).

There are several ketone monitoring devices on the market, which are mainly used for managing diabetes:

- FreeStyle® Optium Neo, which has a choice of tools designed to help people who use insulin.
- Precision Xtra® system and Precision Xtra blood ketone test strips.
- Ketonix® breath ketone monitor, which is a reusable breath ketone analyzer that measures the level of breath ketones. Measurements indicate the acetone in a user's breath, which is produced from the breakdown of acetoacetate in the person's blood, and are highly accurate and reliable.
- Nova Max® Plus glucose and ketone monitoring system.
- Walgreens TRUEresult® system.

In addition, in-body ketone levels can be measured by using urine strips or breath tests. However, it is not possible to measure the most important of the three types of ketone (beta- hydroxybutyrate) using these methods (Felton, 2019).

Findings

The National Institute for Health and Clinical Excellence recommended that children with epilepsy who are unresponsive to anti-epileptic drugs can be referred to a pediatric epilepsy specialist to consider use of the ketogenic diet. No dietary recommendations were made for adults with epilepsy, as no data exist (National Institute for Health and Care Excellence, 2019).

A survey in the United Kingdom and Ireland found the number of centers offering ketogenic diets to treat epilepsy rose from 22 to 39 from 2000 to 2017, with patients treated soaring from 101 to 754. As of early 2020,

another 267 patients are waiting to start ketogenic diets. Centers accepting adult referrals rose from two to seven (Whiteley, 2020).

A practice paper of the Academy of Nutrition and Dietetics on ketogenic diets for epilepsy included an overview of various diets, a brief literature review on efficacy, guidelines for implementation and coordination of care, and the role of registered dietitian nutritionists. Ketone monitoring is not addressed (Roehl, 2017).

A 26-member panel of the International Ketogenic Diet Study Group comprised of pediatric epileptologists and dietitians from nine nations produced a consensus statement on manuscript of the ketogenic diet (Kossoff, 2009). Two physicians from Children's Hospital of Philadelphia developed a treatment algorithm for treating epilepsy, including the ketogenic diet (Abend, 2008). The guideline includes monitoring the patient's condition and treatment, but no specific mention of ketone monitoring was made (Kossoff, 2008).

A more recent guideline mentions ketogenic diet as one of the means of treating children with epilepsy for patients who are pharmacologically resistant (Tolaymat, 2015). Another recent guideline states recommendations for treating infants with seizures using the ketogenic diet (van der Louw, 2016). A systematic review of six studies found superior seizure reduction in the ketogenic diet versus the medium-chain triglyceride diet (limited evidence); and in the classical ketogenic diet versus the gradual diet (moderate evidence) (Araya-Quintanilla, 2016).

A systematic review found 32% of epileptic adults treated with ketogenic diets achieved at least a 50% reduction in seizures, not different from the 29% placed on a modified Atkins diet. The proportions achieving at least a 90% reduction were nine and five percent, respectively, a significant difference. However, even though the effects are long term, they might not outlast treatment. Diets are well tolerated, but 51% and 42% of the ketogenic and modified Atkins diet patients discontinued them before study completion because of their restrictiveness (Klein, 2014).

A systematic review of four studies (n = 289) assessed epileptic experience of children with ketonic diets. Although the studies are not randomized, a high attrition rate was found, as children frequently experience difficulty tolerating the diet (Levy, 2012).

A Cochrane review of seven randomized controlled trials of 427 children and adolescents found relatively similar results between persons with epilepsy on ketonic diets and modified Atkins diets, but cautioned that more research is necessary to confirm these findings (Martin, 2016). Another Cochrane review of people with epilepsy and intellectual disabilities treated by means other than pharmacology found only one study of poor quality (Jackson, 2015).

Another Cochrane review of 11 studies (n = 778) found evidence supporting use of ketogenic diet, but most studies were small. Moreover, no mention was made of measurement of ketone levels through urine and blood – only reduction in seizures and adverse events (Martin-McGill, 2018). An update by the same team (13 studies, n = 932) found evidence suggesting effective use of the ketogenic diet in treatment-refractory epilepsy in children, but found uncertain results among adults (Martin-McGill, 2020).

A meta-analysis of 70 studies of children and adolescents with epilepsy comparing classical ketogenic diet and modified Atkins diet revealed a non-significant trend toward a higher efficacy within the Atkins group at month-

3 and month-6 ($P > .05$). Response rates were insignificantly higher for the ketogenic group, the proportion

achieving ≥ 50% seizure reduction at months 1, 3, 6, 12, and 24 were 62%, 60%, 52%, 42%, and 46%; for the Atkins group, reduction rates at 1, 3, 6, and 12 months were 55%, 47%, 42%, and 29% (Rezaei, 2017).

A systematic review of 45 studies, including seven randomized controlled trials, analyzed rates of adverse effects of the ketogenic diet in children with epilepsy. The most common events included gastrointestinal disturbances (40.6%), hyperlipidemia (12.8%), hyperuricemia (4.4%), lethargy (4.1%), infectious diseases (3.8%) and hypoproteinemia (3.8%). Severe adverse effects, such as respiratory failure and pancreatitis, occurred in under 0.5% of cases. Nearly half of the patients discontinued the diet, primarily because of lack of efficacy, not adverse events (Cai, 2017).

Another systematic review of 45 studies included seven randomized controlled trials that addressed ketogenic diets for child epileptics. Two showed improvements in seizure frequency, and the other five could not compare different types of ketogenic diets. The authors state that no randomized trials exist for adults, and that ketogenic diets are linked with elevated risk of gastrointestinal and other adverse effects (Cross, 2015).

A systematic review of 13 studies (n = 341) assessed treatment of infantile spasms with ketogenic diets. A median of 64.7% of patients experienced a spasm reduction > 50% short term, and 9.54% long term. Spasms of unknown etiology had a better chance of achieving freedom from seizures (risk ratio 1.72) (Prezioso, 2018).

A meta-analysis of 12 studies (n = 270) of pediatric patients with epilepsy documented higher efficacy for all and classical ketogenic diets (42% and 52%) compared to modified Atkins diets (34%). However, compliance rates for ketogenic diets (45% and 38%) were lower than the Atkins rate (56%) (Ye, 2015).

Two recent articles arrived at conflicting determinations about ketogenic diets and epilepsy. A systematic literature review found little support for using the diet in patients with refractory status epilelpticus (Willems, 2020), while a systematic review of 24 articles concluded various forms of ketogenic diets seem tolerable and effective; in each of the 21 articles addressing epilepsy reported seizure reduction after treatment compared to baseline (Christensen, 2021).

Ketone monitoring in urine and blood for compliance with the ketogenic diet may be performed at least daily, at any time. One study suggests that ketonuria is most reliably measured in the early morning and after dinner, as stable ketosis is highest at these times (Urbain, 2016).

One study recommends that monitoring of children with epilepsy on a ketogenic diet should be evaluated every three months during the first year, and every six months during the second year. Side effects to evaluate during monitoring include hyperlipidemia, cardiac disease, growth failure, gastrointestinal disorders, nephrolithiasis/iric acid stones, vitamin and mineral deficiencies, and bone health (Bergqvist, 2012).

A systematic review/meta-analysis of 18 studies of ketogenic diets on epileptic children showed similar efficacy (seizure remission) at three and six months after treatment started, indicating that three-month results are good predictors for longer periods (Liu, 2019).

A systematic review of 18 articles of families of an epileptic child on the ketogenic diet found the dominant quality of life-related psychological factor was the need for counseling for parents and clear expectations on expected outcomes. Non-adherence and dropout rates were high, and the reasons and timing were not well

documented (Poelzer, 2018).

A meta-analysis of 16 studies (n = 338) of adults with drug-resistant epilepsy revealed an efficacy rate of seizure freedom to be 13%; seizure reduction of 50% or more to be 53%; and seizure reduction of 50% or more in adults with intractable epilepsy to be 27%. Adverse reactions were mild, but more common than low glycemic index diet and low-dose fish oil diet (Liu, 2018).

A systematic review/meta-analysis of 33 (n = 534) of infants on the ketogenic diet showed 59% and 33%, respectively, achieved at least half and total seizure reduction. Retention was 84% at three months and 27% at 24 months (Lyons, 2020).

References

On January 19, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “ketogenic diet” and “ketone monitoring.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

2/2016: initial review date and clinical policy effective date: 7/2016

2/2017: Policy references updated.

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