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In a nutshell

Producing ketosis by high fat and low carbohydrate intake appears to significantly reduce seizure frequency in 2/3rds of epileptics unresponsive to conventional drugs.

Side-effects need to be watched for, and data on long-term complications is lacking. Since the evidence is mostly case-series rather than RCTs, caution in implementation along with expert dietetic support is appropriate.

Ketogenic diet for epilepsy

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NUTRITION RESEARCH REVIEW

Study 1: To fast or not

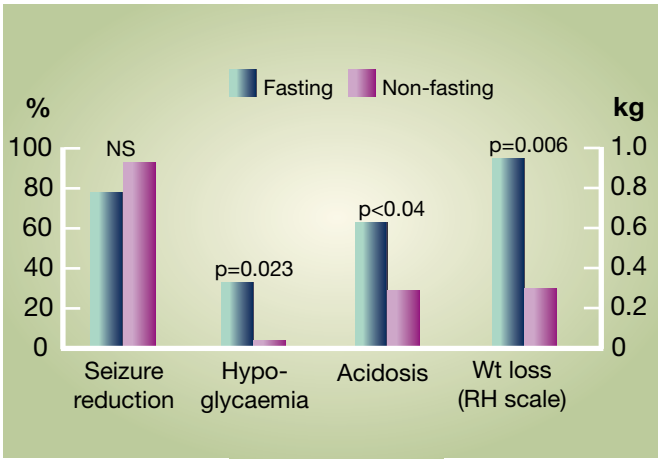
A recent clinical trial compared fasting with non-fasting in the initiating phase of ketogenic diet (KD).

Subjects and method: RCT of 48 children (mean age 5.3 yrs) having seizures at least every 28 days that had not responded to at least 3 antiepileptic drugs (AEDs). The children were put on KD beginning either with or without fasting (up to 48 hours) to establish ketosis.

Results: There was no significant difference between groups in the overall reduction in seizures, proportion with 50% or with 90% reduction. Non-fasting was significantly better than fasting introduction in relation to several parameters - See Graph.

Ref.: Bergqvist AG. et al. Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. Epilepsia. 2005 Nov;46(11):1810-9.

Graph: Non-fasting vs fasting initiation to a ketogenic diet in epileptic children (Study 1)



Study 2: Atkins diet as a basis

A new US trial tested modified Atkins diet in children with intractable epilepsy.

Subjects and method: Prospective uncontrolled trial of 20 children having at least 3 seizures/week, who had been treated with at least 2 AEDs and who had not previously tried Atkins or ketogenic diet. They were put on a diet which limited carbohydrate (10 g/day) and encouraged fat, but did not restrict energy or fluid.

Results: All children developed some degree of ketosis within the first 4 days. At 6 months, 80% were still on the diet, average seizure frequency had decreased from 163 to 40/week (p=0.005). Two thirds had >50% improvement, one third >90% and one fifth were seizure free.

Ref.: Kossoff EH. et al. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. Epilepsia. 2006 Feb;47(2):421-4.

Study 3: Cochrane meta-analysis doesn't go far

A meta-analysis on trials of ketogenic diet in epilepsy identified 20 open studies but failed to find a single randomised placebo-controlled trial.

Ref.: Levy R. et al. Ketogenic diet for epilepsy. Cochrane Database Syst Rev. 2003;(3):CD001903.

COMMENTARY

The ketogenic diet (KD) involves deliberate induction of a ketotic metabolic state through markedly increasing fat and reducing carbohydrate intake (typically resulting in a 4:1 ratio, lower for infants) [1].

Common variations on this theme may include controlling the amount or type of protein intake (to reduce glycogenesis), initial fluid restriction, a short period of fasting, using specifically long- or medium chain fatty acids and energy restriction [1-4].

KD of one kind or another has been advocated as a therapy for epilepsy since at least the 1920's. Indeed, fasting, which causes ketosis, was used to treat epilepsy in ancient times. However, orthodox medicine went through a phase of regarding KD as a treatment of last resort, or even an unproven `alternative medicine' [2, 4-6].

In the last decade orthodox medicine's tune has changed regarding KD. A goodly number of studies have consistently reported success in reducing seizures in a range of epileptic disorders. The level of seizure reduction found in new Study 2 was typical of those other studies [7]. Considering that the majority of the patients had had intractable epilepsy (unresponsive to conventional medication) these have been very good outcomes.

However, as Study 3 highlights, what you will not find are any randomised, placebo-controlled trials. Indeed, there are few controlled trials of any sort, even comparing KD with conventional antiepileptic drugs (AEDs). Most studies have been retrospective case reviews or uncontrolled open prospective trials [3, 8, 9]. A few RCTs are now appearing, most (such as new Study 1) comparing variations in KD protocol, but at least one including placebo control (the results of which are not yet published - see [3]).

Whilst one might think that genuine epilepsy would not be so susceptible to placebo effect, the fact is that in RCTs of AEDs 10-16% of patients in the placebo group experience >50% seizure reduction. That is 20-50% of the magnitude of the impact of the AEDs [10, 11].

Taking this limitation with the evidence base into account, it does still seem clear that KD can be an effective option for intractable epilepsy [1, 9]. And it is a particularly useful option to have, since its effectiveness has been shown in patients unresponsive to conventional medication.

The nutritional aspects of KD in epilepsy coalesce around three main questions:

- How does this diet work, and what does this imply for the nutrient-brain relationship generally?
- What are the essential nutritional elements and do these vary between individual patients?
- How safe is it, and how can side-effects be prevented?

Ketogenic diet induces ketone-based energy metabolism by providing 80%+ of energy from fat

Courtesy of Royal Children's Hospital, Australia

How does it work?

The short answer is: nobody knows [1]. Any diet which alters macronutrient intake balance to such an extent is bound to have multiple metabolic effects, and hence it is not surprising that there have been any number of theories advanced to explain the effect on epilepsy. These concern both what biochemical alterations are responsible and their means of action.

Possible biochemical mediators include amino acids (e.g. glutamate or branched-chain), fatty acids (especially PUFAs), differences in energy yield between fat and carbohydrate metabolism, and direct anticonvulsant properties of ketone bodies. Suggestions for means of action include lowered brain excitability from altered energy metabolism, changes to neurotransmitters (e.g. GABA) or other circulating factors impacting nerve function [1-4, 12-16]. Whether there is a neuroprotective as well as antiepileptic effect is unclear [2]. That being the case, obviously we cannot do much to extrapolate from this to any general conclusions about the nutrient-brain relationship.

What are the essential elements of the diet?

There is uncertainty about exactly what elements of KD are required for maximum effect and hence we lack evidence-based guidelines for customisation to the individual patient. Most experts believe that ketosis is an essential part, although there is only limited evidence of any dose-response relationship with either the amount of ketosis or the fat:carbohydrate ratio [2, 17]. New Study 2 showed that a milder version of Atkins diet producing less ketosis also works. Indeed, positive results from a trial of low glycaemic index diet [18] raises the possibility that carbohydrate restriction on its own could be relevant in KD.

Despite a number of studies investigating the effect of various specific fats (medium-chain fatty acids being more ketogenic than long-chain, for example), no particular clinical advantage of one type or the other has been established [1-3, 19].

What we do know is that this is not a particularly palatable or easy diet to follow long-term [20]. Expert dietetic advice is needed to ensure, for example, that excessive carbohydrate is not inadvertently consumed in medication and to minimise conversion to carbohydrate of glyocogenic amino acids.

New Study 1 found, as have others [21], that initial fasting offers no real advantage, and neither is there any evidence that fluid restriction is necessary. Both facts support the idea of `milder may be better' - an important consideration, particularly since children (in some cases very young infants [22]) are the main target

population for KD in epilepsy. Treatment duration is also largely a matter for individual judgement in the absence of definitive guidelines based on the evidence. Typically KD is maintained for 2-3 years [4]. But whilst animal studies show the antiepileptic action does not outlast the diet [2], human clinical studies have found that seizure reduction can be long lasting, even after the KD was followed for less than a year [4, 23].

Safety factors

KD raises several nutritional safety concerns, and particularly when used long term or with children. Side-effects and complications are commonly reported, and include GI disturbance, hyperlipidaemia, nutrient deficiencies and urinary tract problems - these may well contribute to the not insignificant drop-out rates [1, 4, 24]. Long term safety data (beyond 6-7 years) is sparse, and we do not know, for example, whether such a high fat diet increases risk of CVD in later life.

Micronutrient deficiency is one problem that we should be able to easily avoid by routinely giving appropriate supplements. The elevation of cardiovascular risk from hyperlipidaemia is another matter, although this too might be alleviated by less extreme versions of the diet and by increasing the proportion of medium- and long-chain unsaturated fatty acids that make it up.

Any adverse effect on childrens' growth would certainly be a concern, particularly if there were any impact on brain growth [1, 8, 25]. There is indeed evidence of some negative growth impact from the diet [1, 26], but so far no human evidence showing this has affected children's brain growth or cognition. Common sense suggests this would be less likely when using versions where protein and energy are less restricted.

In summary

Despite the lack of RCTs, the evidence (particularly in children) does strongly suggest a clinically significant effect from KD in reducing seizures in about two thirds of epileptics refractory to conventional medication. A half of those responders (1/3rd of all patients) will be entirely or nearly seizure-free [1]. The practical details of how to implement the diet to obtain the optimal outcome remain more a matter of individual judgement than something we can base on strong trial evidence.

In such a situation, it seems prudent to ensure that the diet is prescribed by clinicians experienced in its implementation, closely supported by dietetic expertise, and that the process proceed as gently and carefully as each individual's clinical situation allows.

Palatability can be an issue with KD, so dietitians and parents need to work together to ensure the child still enjoys their meals

Courtesy of Epilepsy and Brain Mapping Program, Calif, USA (www.epipro.com)

References:

1. Papandreou D. et al. The ketogenic diet in children with epilepsy. Br J Nutr. 2006 Jan;95(1):5-13.
2. Stafstrom CE. Dietary approaches to epilepsy treatment: old and new options on the menu. Epilepsy Curr. 2004 Nov-Dec;4(6):215-22.
3. Freeman J. et al. The ketogenic diet: from molecular mechanisms to clinical effects. Epilepsy Res. 2006 Feb;68(2):145-80.
4. Murphy P. Use of the ketogenic diet as a treatment for epilepsy refractory to drug treatment. Expert Rev Neurother. 2005 Nov;5(6):769-75.
5. Karceski. et al. The expert consensus guideline series: treatment of epilepsy. Epilepsy Behav. 2001; 2:A1–A50.
6. Hemingway C. et al. Changing Physician Attitudes Toward the Ketogenic Diet: A "Parent-Centered" Approach to Physician Education about a Medication Alternative. Epilepsy Behav. 2001 Dec;2(6):574-578.
7. Lefevre F. et al. Ketogenic diet for the treatment of refractory epilepsy in children: A systematic review of efficacy. Pediatrics. 2000 Apr;105(4):E46.
8. Snead OC 3rd. The ketogenic diet: a cautionary note. Pediatr Res. 2004 Mar;55(3):368-9.
9. Thiele EA. Assessing the efficacy of antiepileptic treatments: the ketogenic diet. Epilepsia. 2003;44 Suppl 7:26-9.
10. Burneo JG. et al. Magnitude of the placebo effect in randomized trials of antiepileptic agents. Epilepsy Behav. 2002 Dec;3(6):532-534.
11. Marson AG. et al. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. Epilepsia. 1997 Aug;38(8):859-80.
12. Dahlin M. et al. The ketogenic diet influences the levels of excitatory and inhibitory amino acids in the CSF in children with refractory epilepsy. Epilepsy Res. 2005 May;64(3):115-25.
13. Jirapinyo P. et al. High plasma branched-chain amino acids:aromatic amino acids ratio in children on the ketogenic diet: a mechanism in controlling epilepsy. J Med Assoc Thai. 2004 Apr;87(4):432-7.
14. Yudkoff M. et al. Ketogenic diet, brain glutamate metabolism and seizure control. Prostaglandins Leukot Essent Fatty Acids. 2004 Mar;70(3):277-85.
15. Cullingford TE. The ketogenic diet; fatty acids, fatty acid-activated receptors and neurological disorders. Prostaglandins Leukot Essent Fatty Acids. 2004 Mar;70(3):253-64.
16. Schwartzkroin PA. Mechanisms underlying the anti-epileptic efficacy of the ketogenic diet. Epilepsy Res. 1999 Dec;37(3):171-80.
17. Bough KJ. et al. Higher ketogenic diet ratios confer protection from seizures without neurotoxicity. Epilepsy Res. 2000 Jan;38(1):15-25.
18. Pfeifer HH. et al. Low-glycemic-index treatment: a liberalized ketogenic diet for treatment of intractable epilepsy. Neurology. 2005 Dec 13;65(11):1810-2.
19. Schwartz RM. et al. Metabolic effects of three ketogenic diets in the treatment of severe epilepsy. Dev Med Child Neurol. 1989 Apr;31(2):152-60.
20. Lightstone L. et al. Reasons for failure of the ketogenic diet. J Neurosci Nurs. 2001 Dec;33(6):292-5.
21. Kim DW. et al. Benefits of the nonfasting ketogenic diet compared with the initial fasting ketogenic diet. Pediatrics. 2004 Dec;114(6):1627-30.
22. Klepper J. et al. Introduction of a ketogenic diet in young infants. J Inherit Metab Dis. 2002 Oct;25(6):449-60.
23. Marsh EB. et al. The outcome of children with intractable seizures: a 3- to 6-year follow-up of 67 children who remained on the ketogenic diet less than one year. Epilepsia. 2006 Feb;47(2):425-30.
24. Kang HC. et al. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004 Sep;45(9):1116-23.
25. Zhao Q. et al. Detrimental effects of the ketogenic diet on cognitive function in rats. Pediatr Res. 2004 Mar;55(3):498-506.
26. Peterson SJ. et al. Changes in growth and seizure reduction in children on the ketogenic diet as a treatment for intractable epilepsy. J Am Diet Assoc. 2005 May;105(5):718-25.