

DIETARY THERAPY FOR EPILEPSY: THE ADVANTAGE OF RAPID ONSET OF ACTION

When Do Seizures Usually Improve with the Ketogenic Diet? Kossoff EH, Laux LC, Blackford R, Morrison PF, Pyzik PL, Hamdy RM, Turner Z, Nordli DR Jr. *Epilepsia* 2008;49:329–333. **PURPOSE:** Parents often expect immediate seizure improvement after starting the ketogenic diet (KD) for their children. The purpose of this study was to determine the typical time to seizure reduction as well as the time after which it was unlikely to be helpful in those children started on the KD. **METHODS:** Records of all children started on the KD at Johns Hopkins Hospital, Baltimore, ($n = 83$) and Children's Memorial Hospital, Chicago, ($n = 35$) from November 2003 to December 2006 were examined to determine the first day in which seizures were reportedly improved. **RESULTS:** Of the 118 children started on the KD, 99 (84%) had documented seizure reduction. The overall median time to first improvement was 5 days (range: 1–65 days). Seventy-five percent of children improved within 14 days. In those children who were fasted at KD onset, the time to improvement was quicker (median 5 vs 14 days, $p < 0.01$) with a higher percentage improving within 5 days (60% vs 31%, $p = 0.01$). No difference was identified between fasting and nonfasting in regards to long-term outcomes, however. **DISCUSSION:** The KD works quickly, when effective, typically within the first 1–2 weeks. Starting the KD after a fasting period may lead to a more rapid but equivalent long-term seizure reduction, confirming prior reports. If the KD has not led to seizure reduction after 2 months, it can probably be discontinued.

COMMENTARY

The ketogenic and Atkins diets are potentially effective dietary treatment options for patients with refractory epilepsy (1–3). Both diets restrict carbohydrates and have a high content of fats. The ketogenic diet, but not the Atkins diet, also restricts calories, proteins, and fluids. Both diets are associated with ketosis, which is considered to play a role in

seizure suppression; however, it is not clear that ketosis is always necessary for seizure control (2). The diets can be tedious to follow consistently, and compliance likely is facilitated greatly by the presence of early efficacy. The faster the onset of action, the more likely it is that the diet will be pursued properly.

In their study, Kossoff et al. found that a response to the ketogenic diet was usually very prompt. While the median time to seizure reduction was 5 days overall, some children demonstrated an improvement after only 1 day. Children who were first fasted had a shorter median time to seizure reduction; however, the duration of fasting was not important, as there was no

difference in time to seizure reduction between 1 and 2 days of fasting. Only 10% of patients who benefited had shown no improvement within 23 days; thus, the authors suggested that if the diet was not effective within 2 months, it could be discontinued. However, their 2-month rule had notable exceptions that offer hope to individuals with no other treatment options remaining; four children who had no reported improvement in the first 2 months of the ketogenic diet later had a >50% seizure reduction, and one of them suddenly became seizure-free.

The rapid onset of action of the ketogenic diet was also demonstrated for the Atkins diet in adults. Kossoff et al. investigated the Atkins diet in 30 adults with partial or generalized seizure types (3). For the 18 patients who improved on the diet, the median time until seizure reduction was 2 weeks, with a range of 1 to 8 weeks. Early in the treatment, there was a trend toward higher levels of ketosis being associated with greater improvement in seizure control. Later, there was a correlation between weight loss and diet efficacy. Sixteen individuals stopped the diet before the end of the study, with six of them citing diet restrictiveness as the main reason for discontinuation. In contrast, all 14 individuals who completed the 6-month study continued the diet thereafter. The findings reflect that the demonstration of efficacy is important for compliance with a restrictive treatment such as the Atkins diet, and the earlier the efficacy, the better the compliance is.

A rapid onset of action has several advantages and implications. First, such therapies might be considered before others for patients with very frequent seizures and even for individuals with refractory status epilepticus. Patients in the study of Kossoff et al. had a very high seizure frequency (the mean was 250 seizures per month) and needed a therapy with a rapid onset of action. Few antiepileptic drugs have been evaluated for the speed of onset of action during oral therapy. One new drug that has received a lot of attention in that regard is levetiracetam, which can demonstrate evidence of antiseizure activity within the first 2 days of treatment (4,5). The finding of rapid onset

of action of oral levetiracetam prompted its use in refractory status epilepticus and other acute seizure settings (6). There are rare reports of the successful use of the ketogenic diet for refractory status epilepticus (7). However, it is likely that with the findings of Kossoff et al., the ketogenic diet will be used more often and earlier for patients with frequent, refractory seizures or even those with refractory status epilepticus.

Another important advantage of rapid onset of action is the ability to predict treatment failure rapidly, permitting the patient to move on to the next treatment option in a timely manner. Such knowledge is particularly important for patients who have a high seizure frequency and for those adhering to a restrictive and tedious treatment, such as the ketogenic or Atkins diets.

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