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Dietary and medication adjustments to improve seizure control in patients treated with the ketogenic diet

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Abstract

Unlike anticonvulsant drugs and vagus nerve stimulation, there are no guidelines regarding adjustments to ketogenic diet regimens to improve seizure efficacy once the diet has been started. A retrospective chart review was performed of 200 consecutive patients treated with the ketogenic diet at Johns Hopkins Hospital from 2007-2013. Ten dietary and supplement changes were identified, along with anticonvulsant adjustments. A total of 391 distinct interventions occurred, of which 265 were made specifically to improve seizure control. Adjustments lead to >50% further seizure reduction in-18%, but only 3% became seizure-free. The benefits of interventions did not decrease over time. There was a trend towards medication adjustments being more successful than dietary modifications (24% vs. 15%, $p = 0.08$). No single dietary change stood out as the most effective, but calorie changes were largely unhelpful (10% with additional benefit).

Keywords

diet; ketosis; ketogenic; anticonvulsants; epilepsy

Introduction

The ketogenic diet is a high fat, low carbohydrate diet that is used in the treatment of refractory pediatric epilepsy.¹ Overall, the ketogenic diet has proven to be highly effective in

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Author Contributions

JHS was the principal research investigator and wrote the first draft of the manuscript. EHK was the senior author, director of the ketogenic diet program, assisted with statistical analysis and writing of the manuscript. ZT and SCD were responsible for care of the patients and took part in revising the manuscript.

Declaration of Conflicting Interests

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Ethical Approval

Ethical approval to conduct this study was given by the Johns Hopkins Institutional Review Board.

approximately 40-50% of children started on it^{2,3}. However, some children that begin the ketogenic diet do not respond at all and others improve immediately yet experience seizure recurrence later. In these situations, neurologists and dietitians often attempt to “fine-tune” the ketogenic diet to improve seizure control.

The International Consensus Statement details how the ketogenic diet should be administered⁴, but it primarily addresses side effects and tolerability for ketogenic diet maintenance. At this time, there is only anecdotal evidence of the impact of these “fine-tuning” changes on seizure control. Although an entire chapter of the book *Ketogenic Diets* is devoted to “fine tuning”, few references cite published evidence.⁵ To our knowledge, only four studies to date have assessed the impact of a dietary change to the ketogenic diet to benefit seizures. One study examined the impact of ketogenic ratio changes from a 3:1 (fat: carbohydrate and protein) to 4:1, showing that 10 of 12 patients who were not seizure-free with the 3:1 ratio had further (but not complete) seizure reduction when switched to a 4:1 ratio.⁶ Another study demonstrated that achieving an ideal body mass index did not lead to improved efficacy in 123 children on the ketogenic diet.⁷ The third study examined the effect of adding branched chain amino acids to the ketogenic diet, and found that 47% (8/17 patients) experienced a >50% seizure reduction after the addition of this supplement.⁸ The most recent study evaluated the impact of intermittent fasting, with 4 of 6 children experiencing a 50-99% further seizure reduction.⁹ Alternative ketogenic diets have been created, including the medium-chain triglyceride diet, modified Atkins diet, and low glycemic index treatment¹⁰⁻¹², however, these diets were predominantly created to improve tolerability rather than efficacy.

These small sample sizes and mixed results suggest that further study is needed to examine the relationship between dietary changes and seizure control. Understanding the true value of these changes is very important to parents, neurologists, and dietitians at ketogenic diet centers and may be the most common unanswered practical question in dietary management. The likelihood of improvement would guide decisions regarding additional anticonvulsant trials as well as continuing and altering the ketogenic diet (versus its discontinuation). The purpose of this study is to formally characterize the impact of the changes made during the “fine tuning” process and to determine if any type of intervention is superior.

Methods

Subjects

This study was a retrospective chart review of the most recent 200 consecutive patients with intractable epilepsy who started the classic ketogenic diet at the Johns Hopkins Hospital between October 2007 and June 2013. The study was approved by the Johns Hopkins Institutional Review Board and all families provided informed consent. No patient on the ketogenic diet over this time period was excluded from the study. Patients on the ketogenic diet at the time of study were monitored through follow-up clinic visits every 3 months after starting the ketogenic diet. Between clinic visits, the patients and their families were instructed to keep seizure calendars and to call or email the physicians with any concerns. All phone calls and emails were reviewed in their entirety.

Modifications

Ten dietary/supplement changes were identified as implemented for seizure control by the attending physician. These included increased ketogenic ratio, decreased ketogenic ratio, increased calories, decreased calories, carnitine supplementation, medium chain triglyceride oil addition, a one-time fast before restarting the ketogenic diet, intermittent fasting (twice weekly), changing calorie distribution throughout the day, and removal of artificial sweeteners. Medication dose increases and new anticonvulsant additions made by the physician were also examined. The interventions were noted to be made either primarily for side effects (i.e. intolerability, hunger, growth concerns) or to improve seizure control, but all were included in this analysis in case of potential benefit. If multiple interventions were made at the same time, these were also documented as unique modifications but with the same outcomes. The interventions were made by the physician either at clinic follow-up visits or via phone call or emails with parents if better seizure control was desired in the interval between clinic visits.

Data analysis

Clinic notes, emails, and phone calls were reviewed over the entire ketogenic diet treatment course up to a maximum of 4 interventions per patient. Records were reviewed for patient demographics, ketogenic diet composition, interventions made, timing and outcomes of the interventions, and overall seizure reduction. Patient demographics included age, gender, seizure type, seizure frequency per month, seizure etiology, age at seizure onset, age at ketogenic diet onset, total number of anticonvulsants tried, and number of anticonvulsants at ketogenic diet onset.

The primary outcome was the difference in percentage reduction in seizure frequency compared to the previous time point before the intervention was implemented, all compared to the baseline. For example, a patient with 50% seizure reduction over pre-ketogenic diet who then had 90% seizure reduction after an intervention would be considered a 40% additional improvement. Patients who became seizure-free after modifications were documented separately as such. These outcomes were assessed an average of 1.6 months after interventions were made with a limit of 3 months. The change in seizures was noted either by parental notification through email or phone and then confirmed by the physician at the next outpatient clinic visit. Categorical data were analyzed using Pearson's chi-square. Comparisons of means were analyzed using a two-tailed *t*-test. The significance level for all tests was $p = 0.05$.

Results

Patient characteristics

There was a near equal distribution of males ($n=101$) and females ($n=99$). The seizure types at time of ketogenic diet onset were multiple (54%), infantile spasms (17.5%), partial (15.5%), atonic (4%), tonic-clonic (4%), myoclonic (3%), and absence (2%). The ten most common seizure etiologies included unknown (29), Doose syndrome (25), Lennox Gastaut syndrome (21), Dravet syndrome (9), tuberous sclerosis complex (6), chromosomal abnormalities (6), mitochondrial disorder (6), Ohtahara syndrome (5), Aicardi syndrome (5),

and Rett syndrome (3). One child had Glut-1 deficiency. Of the 200 patients, 62% had at least a 50% improvement at some point on the ketogenic diet, with 29% experiencing prolonged periods of seizure freedom. Further demographics are provided in Table 1.

Intervention Characteristics

Overall interventions—The majority, 156 (78%), had at least one diet or medication intervention made. Of the 44 patients without any adjustment to their ketogenic diet, many came off the diet within 2-4 weeks. Twelve (27%) had no interventions done as they were seizure-free immediately after starting the ketogenic diet and required no adjustment for seizure control. Others had new-onset infantile spasms or were in status epilepticus and the ketogenic diet did not work within 2 weeks so was discontinued¹³, and some found the ketogenic diet to be too restrictive. A total of 391 distinct and occasionally concurrent interventions occurred at 333 contact points.

Interventions done primarily for seizure control—Some of the 391 interventions were not made specifically for seizure control, and instead were made due to reported side effects of the diet. The interventions most often used for side effects included increasing calories (46.7% of the time implemented for side effects) and decreasing the ketogenic ratio (26.2%). When excluding these interventions done primarily for side effects, there were 265 distinct interventions made at 213 contact points and these were then analyzed for true effectiveness. Table 2 shows the frequency of interventions made for seizure control throughout the ketogenic diet duration. Overall, the 4 most common interventions (both dietary and medication) used were increasing the ratio (16.6% of total interventions), adding a new anticonvulsant medication (14.7%), medication dose adjustment (13.6%), and carnitine addition (12.5%). Of the total number of interventions made for seizure control, 71.6% were dietary and 28.4% were medication changes. The average duration of time on the ketogenic diet for the 4 time points when a modification was made was 3.5, 8.0, 11.1, and 14.5 months. As patients remained on the ketogenic diet for longer periods, it was more likely that a medication change was utilized as opposed to a dietary change (Table 2).

Outcomes of Interventions

Of the interventions made specifically for seizure control, overall, 42.4% led to at least a minimal reduction (>1%) in seizure frequency reported by families. In 17.8% the intervention led to at least a 50% additional reduction in seizures, including 7.5% with 90-99% improvement, and 3.3% who achieved seizure freedom. Overall, there was a trend that medication adjustments were more successful than dietary modifications with 24% of medication changes leading to >50% additional seizure reduction compared to 15% of diet changes ($p=0.08$).

Nine interventions led to seizure freedom. These occurred in patients with a mean age of 4.2 years at ketogenic diet onset, with similar etiologies to the other patients in this study, including cryptogenic, myoclonic-astatic epilepsy (Doose syndrome), tuberous sclerosis complex, West syndrome, and stroke. Interventions were also similar to the larger cohort, including added anticonvulsants (clobazam, phenobarbital, and zonisamide; $n=3$), decreased

ketogenic ratio (n=2), one-time fast restart (n=1), increased calories (n=1), carnitine (n=1), and anticonvulsant dose adjustment (oxcarbazepine; n=1).

The percentages of interventions made for seizure control leading to >50% additional seizure reduction across the 4 time points ranged from 13% to 26% (18.1% at time point 1, 13.2% at time point 2, 26.8% at time point 3, and 14.3% at time point 4). There was no significant difference between the outcomes of seizure success at time point 1 vs. time point 4 (p=0.44). The percentages of interventions which led to seizure freedom remained similar for all 4 of the modifications done throughout the ketogenic diet duration.

Outcomes from Dietary Interventions—Of the 107 patients who had at least one dietary intervention made specifically for seizure control, 17.7% had >50% additional seizure reduction and 3.7% became seizure free. No single dietary modification stood out as the best with the interventions more likely to be successful including a one-time fast restart (17.6%) and carnitine addition (17.2%). When the dietary modifications were grouped into calorie, ratio, supplementation, and fasting changes, there was no significant difference in seizure success between any intervention groups (p=0.58). The group with the lowest percentages of additional improvement was calorie changes (10.4%).

Predictors of Dietary Interventions

Upon further examination of the characteristics of the patients who improved after dietary changes, those with >1% additional improvement from a dietary modification had a younger average age when starting the ketogenic diet than the patients with no improvement (3.6 vs. 5.1 years, p=0.02). In addition, they had an earlier average age of seizure onset (1.2 vs. 2 years, p=0.049). There were no differences in seizure frequency, etiology, total number of anticonvulsants tried, gender, or seizure type between these two groups. Of patients with a more significant benefit (>50% additional seizure reduction), only those with a baseline lower seizure frequency did better with dietary modifications (230 vs. 572 seizures per month, p=0.003).

Medication Interventions

There were fewer medication changes than dietary changes. Thirty-four patients (21.8% of those with interventions) had a new anticonvulsant added at least once during their time on the ketogenic diet. The four most commonly added anticonvulsants overall were valproate (n=8), clonazepam (n=7), zonisamide (n=7), and rufinamide (n=4). Improvements of at least 50% additional reduction in seizures with anticonvulsants were seen with clobazam (1 patient of 1), clonazepam (2/7), felbamate (1/1), lamotrigine (1/2), phenobarbital (1/1), prednisolone (1/3), valproate (2/8), vigabatrin (1/2), and zonisamide (2/7).

Discussion

This is the first study to our knowledge that examines the overall impact of multiple methods of fine-tuning the ketogenic diet after initiation to potentially improve seizure control. Making modifications to the ketogenic diet appears to be a common practice at our center, with 78% of patients receiving at least one modification, and we suspect this is true

worldwide. Studies have shown that if the ketogenic diet is going to reduce seizures, it will usually show benefit within 2 weeks, although continued improvement may occur after that time.¹⁴ Our study suggests that once the ketogenic diet is started and seizure improvement occurs, but seizure freedom is not achieved, our neurologists most often will frequently make dietary modifications.

We identified 10 dietary changes that were commonly used at our center. Typically the first type of modification made was to the ketogenic dietary composition (i.e. changing the ketogenic ratio or calories), possibly due to previous published evidence.⁶ The second intervention often involved adding a supplement (carnitine addition or medium chain triglyceride oil); suggesting that the ketogenic diet team believed the diet itself was fully optimized after 6-8 months. Next, a more non-traditional modification was then implemented (intermittent fasting, redistribution of calories throughout the day). Medication changes were often done as a final option, possibly because of a parental bias against anticonvulsants or as a prelude to ketogenic diet discontinuation. This process illustrates a reasonable algorithm for trying modifications to the ketogenic diet.

It does appear that modifications to the ketogenic diet can have some impact on seizure control. Overall, 18% of modifications led to a significant additional seizure reduction. This finding suggests that an adjustment to the ketogenic diet may have an impact, although modest. Nearly all the patients in this series had very severe and intractable epilepsy, and therefore, it is important for patients and their families to realize that seizure freedom after fine tuning is unlikely. We also found that there was a similar chance of improvement even after many months and up to 4 modifications. This suggests that patients who have been on the ketogenic diet for months to years, and have already had some modifications, should not be discouraged from additional changes, rather than either maintaining the ketogenic diet status quo or discontinuing it.

Of the dietary interventions (or anticonvulsant changes), no one stood out as the most effective. However, changing calories had the least percentage of all of the dietary interventions in leading to successful seizure reduction. This finding confirms a previous study examining ideal body mass index and the ketogenic diet, which found that calorie changes to achieve an ideal body mass index did not lead to improved seizure control.⁷ Perhaps, this finding suggests that other dietary changes should be tried before caloric modifications, and calories should be adjusted by dietitians primarily for hunger and weight purposes.

We also examined characteristics of the patients who were most likely to respond to dietary modifications. It appears that younger children starting the ketogenic diet and patients who started having seizures at a younger age were most likely to benefit from a change. A possible explanation is that older patients can achieve ketosis more quickly and are more easily able maintain consistently high levels of ketosis whereas younger children might need more ketogenic diet adjustment. Patients with fewer seizures per month at ketogenic diet onset were more likely to see significant seizure reduction after a dietary change; however, the reasons for this are not clear.

Many families decide to try the ketogenic diet in order to avoid adding multiple new medications and to possibly wean their children off anticonvulsants.¹⁵ Although parents are sometimes reluctant to add medications while maintaining the ketogenic diet, our study suggests that medication changes are at least as effective as dietary ones. Parents should be counseled that if a medication adjustment has to be made, this does not necessarily indicate that the ketogenic diet is ineffective and must be stopped. Previous studies have indicated that zonisamide in combination with the ketogenic diet at the start of the ketogenic diet is more effective than other anticonvulsants, especially phenobarbital.¹⁶ However, of the medications added while actually on the ketogenic diet, no single medication was the most effective. However, the numbers of any one individual anticonvulsant were very few and no firm conclusions can be drawn from this data.

Our study has several limitations. This was a retrospective review that relied on parental reports of seizure reduction. Occasionally, multiple interventions were implemented at the same time, making it difficult to determine which adjustment was responsible for the subsequent change in seizure control. A prospective, randomized study of specific interventions with carefully constructed seizure calendars would be ideal. Also, it is possible that other dietary interventions could be beneficial, such as adding branched chain amino acids or ketone esters, interventions that were not investigated here.^{8,17} Another limitation is that the average time of the first modification was 4 months. It is possible that earlier interventions, occurring during a potentially “critical period” of ketogenic diet adjustment shortly after its initiation (e.g. first month), may yield better results. Finally, with this retrospective study, it was not possible to have a control group without interventions. In our cohort, the patients with no adjustments primarily all discontinued the ketogenic diet prior to one month due to lack of success in an emergency setting (e.g. status epilepticus or new-onset infantile spasms). With no control, it is difficult to determine if the 18% of modifications that led to additional success could have been related to the natural history of seizure fluctuations. These results are somewhat similar to the placebo rates seen in trials of adjunctive anticonvulsants for Lennox-Gastaut syndrome in children, which range from 15.7-32%.¹⁸ However, this may not necessarily be an accurate comparison as these patients had the ketogenic diet modified (and thus our 18% represents those with additional improvement), and a more accurate comparison would be increasing the dose of a daily anticonvulsant.

Conclusion

In summary, “fine-tuning” the ketogenic diet in our series led to significant additional improvement for 1 in 5 patients, even after up to 14 months on the diet. No one dietary or medication modification appeared ideal for improving seizure control, although calorie changes were generally unhelpful. The order of changes implemented, starting with diet modifications, followed by adding supplements, intermittent fasting, then finally adding a new anticonvulsant seems appropriate. These findings can help guide clinical recommendations for fine-tuning the ketogenic diet and give patients and families a realistic sense of what they can expect from the fine-tuning process. Further examination of the methods of managing the ketogenic diet may help provide additional insights to help improve its efficacy.

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Table 1

Patient demographics at baseline (n=200).

Demographics	Average (Range)
Ketogenic diet duration (years)	1.1 (0.1-4.5)
Age at seizure onset (years)	1.6 (0-14)
Age at ketogenic diet onset (years)	4.3 (0.1-21)
Number of anticonvulsants tried	4.3 (0-13)
Number of anticonvulsants at ketogenic diet onset	2.2 (0-6)

Table 2

Intervention frequency made for seizure control at each of four time points (percentage). Top scores for each —time point highlighted in bold font.

Intervention	1 (n=104)	2 (n=86)	3 (n=51)	4 (n=24)
Increasing ratio	22.1	12.8	13.7	14.2
Carnitine addition	12.5	16.3	7.8	14.2
Increasing calories	11.5	8.1	5.8	4.8
Decreasing calories	10.5	9.5	5.8	4.8
Medium chain triglyceride oil addition	5.7	8.1	9.8	0
Decreasing ratio	3.8	5.8	3.9	14.2
Spacing meals	1.9	4.6	0	4.8
One time fast restart	10.5	3.5	5.8	0
Intermittent fasting	1.9	1.2	3.9	14.2
Remove artificial sweetener	0.9	1.2	0	0
Medication dose adjustment	11.5	9.3	25.4	14.2
Medication addition	6.7	19.8	17.6	28.6