



# Factors Affecting the Efficacy, Tolerability and Compliance of Dietary Therapy for Epilepsy- Four-Years Experience

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## Abstract

**Objective:** To evaluate the clinical effectiveness of the Ketogenic Diet (KD) in children as measured by: seizure reduction rates, patient side effects, patient tolerance, and compliance of 2 forms of the KD, the classical and modified Atkins KDs (MAKD).

**Study Design:** A single-centre, retrospective study of 43 children with Intractable Epilepsy (IE) commencing the KD between 2012 and 2015. We assessed patient demographics, history of epilepsy, nutritional management, side effects of the KD, growth parameters and biochemistry records. Compliance and tolerance of the KD were explored by recording reasons for modification and cessation.

**Results:** The median age at initiation was 3 years 10 months (range 4 months to 12 years), and the median duration of therapy was 1 year and 4 months. Twenty-five of 43 children (58%) had epileptic encephalopathies. Thirty-five (81%), 26 (60%) and 18 (42%) of children remained on the diet at 3, 12 and 24 months. Of those, 7 (16%), 4 (9%) and 5 (12%) achieved seizure freedom, and 20 (47%), 15 (35%) and 10 (23%) patients achieved >50% reduction in seizures at 3, 12 and 24 months respectively. Seizure reduction was significantly associated with diet duration ( $p < 0.005$ ), and reduction in anti-epileptic medications ( $p < 0.005$ ). Reasons for diet discontinuation included no improvement in seizures (26%), poor compliance (9%), adverse effects (9%) and weight loss (9%).

**Conclusion:** The classical KD and MAKD provide comparable seizure control, seizure freedom and reduction in medication, particularly for those who commit to remaining on the KD out to 24 months.

**Keywords:** Patient compliance/adherence; Diet persistence; Adverse effects; Treatment outcome; Modified atkin's diet

## Abbreviations

AED: Anti-Epileptic Drug; IE: Intractable Epilepsy; KD: Ketogenic Diet; MAKD Modified Atkin's Ketogenic Diet; MCT: Medium-Chain Triglyceride

## Introduction

The Ketogenic Diet (KD) is a medically supervised high fat, low carbohydrate and adequate protein diet that is used to treat children with Intractable Epilepsy (IE), defined as those who continue to experience seizures despite treatment with at least two tolerated and appropriately dosed Anti-Epileptic Drugs (AEDs) [1,2]. The classical KD provides a ratio of grams of fat to grams of carbohydrate and protein combined, and is usually in a ratio of 4:1. Modern versions of the KD are available such as the Medium-Chain Triglyceride (MCT) diet, the Modified Atkins Ketogenic Diet (MAKD) and Low Glycemic Index Treatment (LGIT) which allow for greater palatability and flexibility with meals. This appeals to adolescent and adult populations, whilst still maintaining efficacy in controlling seizures [3-6]. The exact physiology of how the KD induces an anti-epileptogenic state is unclear [7]. Several mechanisms have been postulated, including the anticonvulsant effects of ketone bodies that are produced by fatty acid oxidization, the activation of KATP channels via the suppression of glycolysis which leads to hyperpolarisation of neurons, and inhibition of the intracellular rapamycin (mTOR) signaling pathway [8-10]. The effectiveness of the KD is documented in mainly uncontrolled prospective and retrospective trials, and have

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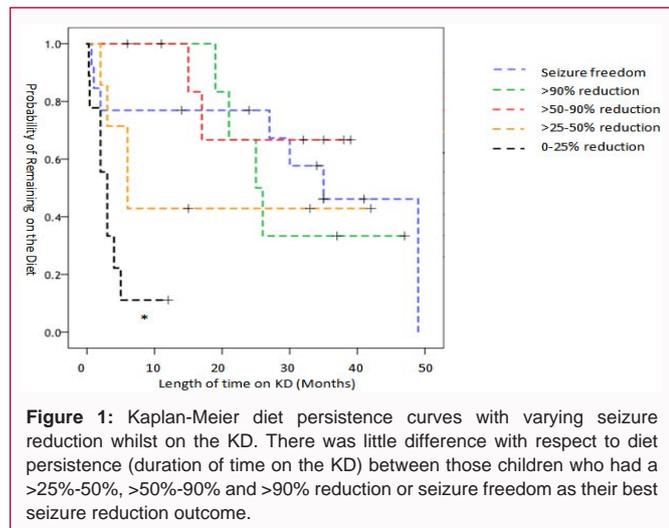
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shown KDs reduce seizure frequency by >50% in over 50% of treated children [11-15]. The literature is limited by the heterogeneity of study methodology and difficulty in evaluation of the long-term benefits of the KD due to the high-risk of performance and detection bias [16]. It is well documented that compliance is a major difficulty with the KD. Low compliance and high drop-out rates have been attributed to adverse side effects such as gastrointestinal disorders, biochemical disturbances and poor growth, poor tolerability of unpalatable meals in children, and challenges faced by parents including time constraints and food preparation [7,17,18]. A meta-analysis of 1084 children from 19 studies found the odds ratio of achieving >50% seizure reduction amongst children who complied with the KD, relative to those who discontinued the diet, to be 2.25 [14]. However, these results may overestimate seizure control when remaining on the KD, as the primary reason for KD discontinuation in 47% of children, was achieving <50% seizure reduction. In addition, the meta-analysis notes that the analysis of dropouts is often variable and unsatisfactory; therefore the clinical characteristics of children at a higher risk of discontinuing diet are unclear. In our previous paper, the predominant ketogenic diet used was the classical ketogenic diet and MCT diet. In this present study up to a quarter of the patients were transitioned to the MAKD after commencing the classical ketogenic diet. The aim of this study is to compare the clinical effectiveness of the classical KD and MAKD (with and without the addition of MCT oil) by monitoring seizure reduction rates, patient side effects, patient tolerance and patient compliance and to illustrate the advantages and disadvantages of the classical and MAKD as regards to growth and side effect profile.

**Methods**

**Ethics approval**

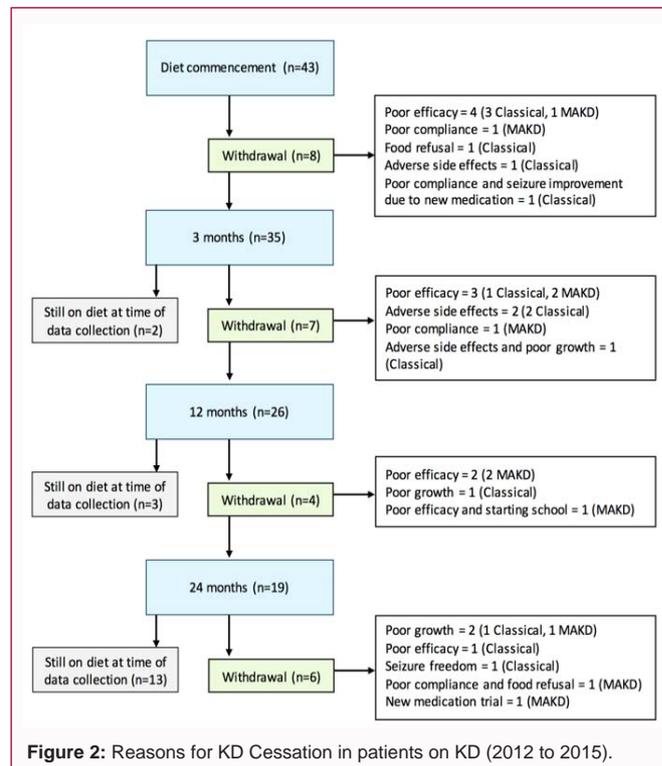
Ethics approval was provided from The Sydney Children’s Hospital Network ethics committee (LNR/12/SCHN/198). Patient names and medical record numbers were de-identified and stored on separate databases to ensure patient confidentiality.

**Recruitment**

The retrospective chart review included all pediatric patients (aged 0 to 18 years) with IE who commenced the KD at Sydney Children’s Hospital Randwick (SCH) between 2012 to 2015.

**Outcome measures**

Patient demographics, seizure frequency and response



rates, epilepsy and medication history, nutritional and dietetic interventions, side-effects and anthropometric data were reviewed. Compliance and tolerability of the KD were assessed by examining reasons for diet modification and cessation as described in the medical records. Seizure reduction at 3, 12 and 24 months post KD initiation was calculated from clinician records and expressed as a percentage (frequency of current seizure burden divided by seizure frequency at baseline) and then categorized as: 0 to 25%; >25% to 50%; >50 to 90%; >90% and seizure freedom. All seizure types were combined for this analysis. Additionally, the greatest seizure reduction for each child during the course of the KD (at any time during the KD) was noted as well as the time of cessation. In the case of two patients who trailed the KD on two separate occasions, only data related to their second attempt was analyzed as both had ceased the first diet trial prior to 2012. Exclusion criteria only applied to analysis of side effects. Children with pre-existing medical conditions and abnormal biochemical anomalies prior to the commencement of the KD were excluded.

**Data analysis**

Statistical analyses were conducted using IBM SPSS version 22. P-values <0.05 were considered statistically significant. Non-parametric (Mann Whitney-U and Kruskal-Wallis) tests were conducted to assess differences in seizure reduction and cognitive improvement with diet duration or age. The Shapiro-Wilk Test was used to test normality of data distribution. Fisher’s Exact Test was used to establish statistical differences between seizure reduction with diet type and other outcome measures. The Wilcoxon signed-rank test was used to determine any median decrease in AED prescriptions. Kaplan-Meier survival curves were performed to analyze retention on the diet with relation to seizure reduction rates and the Mantel Log Rank Test was used to compare subgroups.

**KD initiation protocols**

For the purposes of this study, the term KD collectively refers

**Table 1:** Demographics and characteristics of the study population.

Demographics	n=43
Females, n (%)	22 (51.2)
Age at first seizure (months), Median (range)	6 (0-120)
Age at commencement of KD (months), Median (range)	46 (4-145)
<b>Seizure aetiology, n (% of study population)</b>	
Unknown	12 (27.9)
Genetic	17 (39.5)
Tuberous sclerosis complex	5 (11.6)
Myoclonic Astatic epilepsy (Doose syndrome)	4 (9.3)
CDKL-5 mutation	1 (2.3)
STXBP1 mutation	1 (2.3)
CACNA1A gene mutation	1 (2.3)
Other	5 (11.6)
Structural	10 (23.3)
Hypoxic ischaemic injury	5 (11.6)
Cortical malformation	3 (7.0)
Post-infectious	1 (2.3)
Traumatic brain injury	1 (2.3)
Metabolic	3 (7.0)
GLUT-1 deficiency syndrome	3 (7.0)
Infectious	1 (2.3)
Viral herpes encephalitis	1 (2.3)
<b>Epileptic encephalopathies</b>	
Infantile Spasms	8 (18.6)
Lennox-Gastaut Syndrome	4 (9.3)
Severe Myoclonic Astatic epilepsy (Doose Syndrome)	2 (4.7)
ESES/CSWS	1 (2.3)
FIRES	1 (2.3)
Symptomatic generalised epilepsy (NOS)	9 (20.9)
<b>Change in number of AED prescriptions, n (%)</b>	
Decreased	14 (32.6)
No change	24 (55.8)
Increased	5 (11.6)
<b>Ketogenic diet type at commencement</b>	
Classical	36 (83.7)
4:1	24 (55.8)
3.5:1	3 (7.0)
3:1	5 (11.6)
2.75:1	1 (2.3)
2.5:1	1 (2.3)
Unknown	2 (4.7)
MAKD	6 (14.0)
MAKD with MCT oil	1 (2.3)
<b>Method of feeding</b>	
Orally	31 (72.1)
Enteral	6 (14.0)
PEG	4 (9.3)
NG	1 (2.3)

PEG and NG	1 (2.3)
Oral and Enteral	6 (14.0)

GLUT-1: Glucose Transporter 1; ESES/CSWS: Encephalopathy with Electrical Status Epilepticus during Sleep/Continuous Spike and Waves During Slow Wave Sleep; FIRES: Febrile Infection Related Epilepsy Syndrome; NOS: Not Otherwise Specified

to all forms of the KD including the classical KD, MAKD, with or without the addition of MCT oil. The KD initiation protocols are described in Appendix 1.

## Results

### Patient demographics

Table 1 summarizes the characteristics of the study cohort. Seizure aetiology was genetic or unknown in the majority of children. The most severe epilepsy phenotypes predominate in this study group with 58% having epileptic encephalopathies. The vast majority of patients were commenced on the classical KD (83.7%), however 10 (23.3%) made the transition to the MAKD after a median of 14 months (range 2 to 34 months).

### Ketogenic diet and seizure reduction

Median duration spent on the KD was 17 months (range 8 days to 49 months). Diet type at 3, 12 and 24 months was recorded and categorized according to seizure reduction outcome (Table 2). An estimate of the child's best seizure outcome at any time whilst on the KD was recorded regardless of diet type. Both diets were efficacious with no significant association between KD type and seizure reduction at 3 months, 12 and 24 months ( $p > 0.05$ ). Seizure reduction was not related to age, gender, epilepsy aetiology, presence of epileptic encephalopathy or feeding method ( $p > 0.05$ ). Diet duration was significantly related to the extent of seizure reduction ( $p < 0.005$ ). Figure 1 (online only) shows the Kaplan-Meier diet persistence curves with varying seizure reduction achieved whilst on the KD. Not surprisingly, those with only a 0% to 25% reduction in seizures as their best outcome at any time point were significantly more likely to discontinue the KD compared to those who achieved greater seizure reductions [ $>25$  to 50% ( $p < 0.05$ );  $>50$  to 90% ( $p < 0.001$ );  $>90$ % ( $p < 0.001$ )], or complete seizure freedom ( $p < 0.005$ ). Importantly, the length of time on the KD was not significantly different between those patients with  $>25$ % to 50% seizure reduction compared to those with  $>90$ % seizure reduction or seizure freedom.

### AED prescriptions

KD efficacy can also be assessed using medication reduction. Patients were prescribed a median of 3 AEDs at commencement and cessation of the KD (or at data collection if still on the KD). There was a trend toward patients reducing medications. Fourteen patients (30.2%) reduced their number of medications; however 5 patients (11.6%) required an increase. There was a significant association between change in the number of AEDs prescribed during KD treatment and greatest seizure reduction outcome at any point in time ( $p < 0.005$ ), meaning as patients gained greater seizure control; they were able to reduce their number of AEDs.

### Compliance and tolerability

For the 36 patients who commenced the Classical KD, 11 (25.6%) changed ketogenic ratios whilst remaining on the same KD type, and 10 (23.3%) patients changed from the Classical KD to MAKD after a median of 14 months (range 2 to 34 months). One (2.3%) patient on the MAKD added MCT oil at 9 months. These changes were

**Table 2:** Seizure reduction at 3, 12 and 24 months for children treated with the classical KD and MAKD.

	3 mo		12 mo		24 mo		Greatest seizure reduction at any point**
	Classical	MAKD	Classical	MAKD	Classical	MAKD	
No. on diet, n (%)	29 (67.4)	6 (14.0)	20 (46.5)	6 (14.0)	13 (30.2)	6 (14.0)	43 (100)
Seizure freedom	5 (11.6)	2 (4.7)	3 (7.0)	1 (2.3)	4 (9.3)	2 (4.7)	13 (30.2)
>90%	5 (11.6)	1 <sup>†</sup> (2.3)	6 (14.0)	1 (2.3)	1 (2.3)	0	7 (16.3)
>50% to 90%	7 (16.3)	0	3 (7.0)	1 (2.3)	2 (4.7)	2 <sup>†</sup> (4.7)	7 (16.3)
>25% to 50%	4 (9.3)	1 (2.3)	5 (11.6)	2 <sup>†</sup> (4.7)	2 (4.7)	2 (4.7)	7 (16.3)
0% to 25%	8 (18.6)	2 (4.7)	3 (7.0)	1 <sup>†</sup> (2.3)	4 (9.3)	0	9 (20.9)
Discontinued diet	6 (14.0)	2 (4.7)	12 (27.9)	5 (11.6)	16 (37.2)	8 (18.6)	

<sup>†</sup>Indicates a patient was using MAKD with additional MCT oil (one patient was on the MAKD with additional MCT for the entire duration of the diet (>24 months), and one patient commenced the MAKD and added additional MCT oil at 9 months, and continued on this diet until 14 months at the time of data collection)

\*\*Describes the greatest seizure reduction achieved at any time point for each child regardless of diet duration and diet type

**Table 3:** Summary of (a) reasons for diet cessation, by diet type and of (b) Side-effects of the Classical, Modified Atkins ketogenic diets and combinations.

**3a:** Reasons for diet cessation, by diet type.

Reason for diet cessation	Diet Type	
	Classical (n=14)	MAKD (n=11)
No improvement in seizures (n=11, 25.6%)	5	6 <sup>#</sup>
Poor parental compliance (n=4, 9.3%)	1 <sup>†</sup>	3 <sup>*</sup>
Adverse side-effects (n=4, 9.3%)	4 <sup>+</sup>	-
Poor growth/weight loss (n=4, 9.3%)	3 <sup>+</sup>	1
Food refusal (n=2, 4.7%)	1	1 <sup>^</sup>
Seizure Freedom (n=1, 2.3%)	1	-
Seizure Improvement (n=1, 2.3%)	1 <sup>†</sup>	-
Other (n=2, 4.7%)	-	2 <sup>#</sup>

**3b:** Side-effects of the Classical, Modified Atkins ketogenic diets and combinations.

Side Effect	n	%	Classical (n=26)	Classical changed to MAKD (n=10)	MAKD (n=5)	MAKD with MCT (n=2)
Hypercholesterolaemia	20	46.5	12	5	1	2
Hypercalciuria	19	44.2	12	4	1	2
Constipation	18	41.9	13	3	2	-
Hypertriglyceridaemia	18	41.9	10	7	1	-
Vomiting	12	27.9	8	2	1	1
Diarrhoea	7	16.3	5	2	-	-
Hypoglycaemia	6	14	5	1	-	-
Hyperparathyroidism	6	14	4	-	1	1
Lethargy	4	9.3	3	-	1	-
Iron Deficiency	4	9.3	2	2	-	-
Hypocarnitinaemia	3	7	3	-	-	-
Osteopenia	3	7	3	-	-	-
Dehydration	2	4.7	2	-	-	-
Nephrocalcinosis	2	4.7	2	-	-	-
Metabolic Acidosis	1	2.3	1	-	-	-
Gastroesophageal reflux disease, low vitamin D or hypomagnesium, n=0						

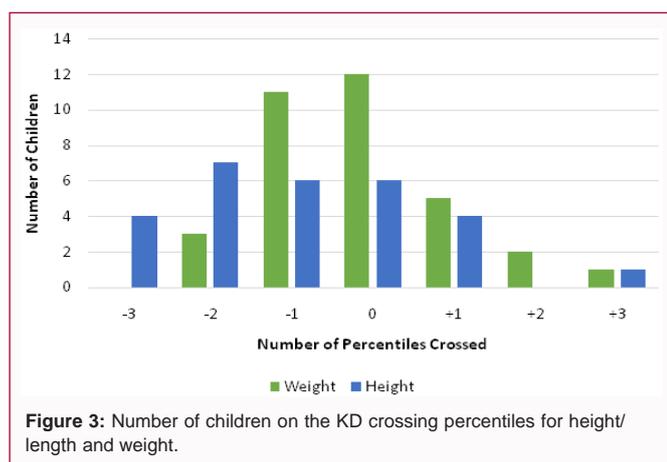
<sup>†</sup><sup>\*</sup><sup>#</sup>Same patient with 2 reasons for cessation

Adverse side-effects: vomiting (n=2), constipation (n=1) and diarrhoea (n=1)

Other: new drug trial (n=1), starting school (n=1)

mostly to improve seizure control (n=10, 23.3%) or encourage food intake (n=6, 14%). Other reasons for dietary modification included management of: weight gain (n=2, 4.7%), side-effects (n=1, 2.3%), high blood ketone (n=3, 7%); and gradually decreasing the diet

ratio when weaning off the KD after >2 years (n=2, 4.7%). Reason for dietary modification was unknown for 2 (2.3%) patients. Some children had dietary modifications for more than one reason. Eight (18.6%), 17 (39.5%) and 24 (55.8%) children had ceased the KD at 3,



12 and 24 months respectively, and one after 24 months (Figure 2). The reasons for cessation are noted in Table 3a. Four (9.3%) patients recorded a combination of 2 reasons for diet cessation.

### Side-effect profile

The most common side effect was hypercholesterolemia ( $n = 20$ , 46.5%), followed by hypercalciuria ( $n=19$ , 44.2%), constipation ( $n=18$ , 41.9%) and hypertriglyceridemia ( $n = 18$ , 41.9%) (Table 3b). Vomiting ( $n=12$ , 27.9%) and diarrhoea ( $n=7$ , 16.3%) were also common, although mainly in those who commenced the classical KD. Six (14%) patients experienced hypoglycemic episodes during initiation of the classical KD (including one who then switched to the MAKD at 15 months), however no child suffered hypoglycemia when commencing the MAKD. Potassium citrate was prescribed to at least 40 patients (93%). Other commonly used supplements included multivitamins ( $n=32$ , 74.4%), calcium with added vitamin D ( $n=21$ , 48.8%), iron ( $n=12$ , 30.2%) and folate ( $n=6$ , 14%).

### Growth

Thirty-four children (79.1%) had serial weight percentiles measured at least 3 months apart after commencing the KD. Eight of the 9 who did not have serial measurements had already ceased the diet before 3 months. Across the duration of the KD, 12 children (27.9%) tracked along their growth percentiles, 8 (18.6%) had an increase in weight that crossed at least 1 percentile, and 14 (32.6%) had a decrease in weight that crossed at least 1 percentile on their growth chart (Figure 3, online). Only 2 children (4.7%) who lost weight returned to their original percentile before ceasing the KD. Of the 18 children still continuing on the KD at 24 months, 5 (11.6%) had a decrease in weight that crossed over 2 percentiles. Children continuing the KD beyond 24 months did not experience significant weight change (as defined as crossing at least 2 or more weight percentiles). Twenty-eight children (65.1%) had serial height/length percentiles measured at least 3 months apart after commencing the KD. Six (14%) of these children tracked along their height/length percentiles for the duration of the KD. A total of 17 children (39.5%) were noted to have deceleration in height/length growth, with 6 (14%), 7 (16.3%) and 4 (9.3%) children decreasing by 1, 2 and 3 height/length percentiles respectively on their growth chart whilst on the KD. Five children (11.6%) had acceleration in height/length growth (Figure 3).

## Discussion

Results from this study suggest the classical and MAKD diets are equally effective treatments for IE, including epileptic encephalopathies [12]. In our cohort, patients who experienced

seizure reduction or control whilst on the KD generally tolerated and complied with treatment and there was a trend towards a reduction in the number of prescribed AED's. In addition, diet duration was associated with seizure reduction as reported by clinicians. These findings appear to be consistent with results of a meta-analysis that included 38 retrospective and prospective studies of the KD as a treatment option for epilepsy at 3, 6 and 12 months [19]. Few studies report outcomes for children treated for 24 months, however our results report long-term efficacy of the KD in over one quarter of the total cohort [11,13]. Eleven of 19 patients (58%) had  $\geq 50\%$  seizure reduction at 24 months, including 6/19 (32%) with seizure freedom which is somewhat better rates than obtained in a previous multicentre study [11]. In our study, age, sex and epilepsy aetiology did not contribute to efficacy of the KD, in keeping with previous studies [11, 20]. Seizure reduction was significantly influenced by diet duration and similar findings have been reported elsewhere in the literature [14,20,21]. However, in a previous study at our centre this was not borne out [12]. Our study adds further weight to the idea that experiencing a positive outcome at some point during diet therapy motivates families to continue the diet. Epilepsy and AEDs can independently negatively impact on cognition and behavior [22]. This impact is likely to be more potentially harmful on the developing child. Children with IE have a higher proportion of cognitive problems than children with well controlled epilepsy [23]. These children may have further cognitive impairments associated with poly-therapy and high AED dosages usually necessary to treat IE [23]. The KD appears to be beneficial as it was associated with a reduction in the number of prescribed AEDs in 14 out of 43 (33%) patients. Neuropsychological assessment data was not included as part of the retrospective chart review, hence formal analysis of cognitive improvement attributable to the diet is not possible in this study. However, cognition is an increasingly recognized and important outcome of the KD and requires further research to quantify impact [24,25]. The authors suggest further prospective neuropsychological studies should be undertaken in any child commencing KD, while appreciating the difficulties in accurately assessing children with severe neurological handicap, a feature frequently seen in children with epileptic encephalopathies. Thus far, KD studies have used functional assessments such as the Gesell developmental scales to assess neurodevelopmental improvements; however these also have limitations [24]. In keeping with the literature mild gastrointestinal symptoms were commonly reported side effects [26]. New onset hypercholesterolemia, hypertriglyceridemia and hypercalciuria were also prevalent in our cohort. Rates of reported dyslipidemia in children treated with the KD across the literature range from 4% to 60% [11,14,26,27]. The long term impact of this is unclear but there are concerns regarding future cardiovascular damage [28-32]. There is also uncertainty at what levels dyslipidemia becomes of clinical significance. Forty of the 43 (93%) children in this study were supplemented with potassium citrate; hence our rates of nephrocalcinosis and kidney stones were relatively low. We assessed tolerability by exploring the reasons for diet changes and cessation rates. Firstly, change in diet type was common. We noted that there were a higher proportion of side effects in those who had used the classical KD compared to the MAKD in the chart review, suggesting the MAKD is more tolerable. The decreased tolerability and increased side effects of the classical KD compared to the MAKD is consistent with the findings of Kim et al., [6] especially with regards to hypercalciuria, nephrocalcinosis and osteopenia. In our cohort, no patients who commenced the MAKD changed to the classical KD or

ceased the MAKD due to side effects. This compares with 4 out of 14 (29%) patients who ceased the classical KD due to side-effects. Rates of compliance at 3, 12 and 24 months in this study are comparable with the literature [11,13,20,21]. The most frequent reason for discontinuing the diet was poor diet efficacy and this has been previously reported [11,14,20]. The KD was generally well tolerated in our population. Only 2 (4.7%) children stopped the diet due to food refusal. Regular follow-up and dietary modifications were made to improve seizure control and food intake, with encouragement of children to remain on the diet. Monitoring the growth of children on the KD is essential [28]. This study found that several patients had deceleration in height/length and in weight. A limitation of this study was that clinicians did not frequently report height/length data in the charts. However, this reflects the difficulty in assessing the height/length of neurologically handicapped children [12]. This study is not without limitations. Complete data was not available for all patients in the chart review. The inconsistent number of patients on each diet, the change in diet at different time points, and the additional of MCT oil to 2 patients contributed to variability in the statistical analyses. The small sample size may have affected the power to detect significance and the retrospective nature of our study may reduce the generalizability and transferability of findings. Reassuringly however, our sample size and findings are similar to previous studies [12,13,20]. Although growth of the children was not a primary aim of this study, this was not evaluated prospectively. We were unable to assess whether catch up growth was achieved in the patients who had weight loss once patients came off either the classical or MAKD. However this study demonstrated that 27.9% of the children actually tracked along their centiles for weight and a further 18% had increased in their weight centiles. As in all retrospective studies, the data was not complete. We acknowledge that catch up growth was not formally assessed and that this is a limitation of our study. Clearly this needs to be addressed in future prospective studies. Longitudinal, prospective, multi-centered studies with larger cohorts would greatly add to the available literature by providing greater power to analyze data and longer-term follow-up data to accurately assess seizure reduction, side effects and growth patterns of children on the KD. Outcomes that warrant further evaluation include sustainment of AED reduction over time, seizure and cognitive improvement after ceasing the diet, and the long-term effects on health and growth [26,29,30]. Additional areas of research into predicting success with the KD can also be analyzed, such as examination of quality of life parameters, formal comparison of neurocognitive and developmental assessment before and after experience of the diet, and socioeconomic status [17,18,24].

### Appendix 1: Initiation Protocols of the KD

Children over the age of 12 months that do not require enteral feeding are generally elected for the MAKD, and children less than 12 months or those children fed entirely are selected for the classical KD. Patients commencing both the classical KD and MAKD at SCH are screened for contraindications. Absolute contraindications include inborn errors of fat metabolism and relative contraindications are the inability to maintain inadequate nutrition and caregiver noncompliance. Baseline biochemistry is obtained as described in the international KD guidelines [31]. Patients undergo a full nutritional assessment including a 3-day nutritional diary to assess their caloric intake and micronutrient requirements. The classical KD is initiated as previously described in Wibisono et al., [12]. Patients on the classical KD are admitted for 5 days as an inpatient without fasting. The dosage of the classical KD is commenced at a ketogenic ratio (grams of fat:

grams of carbohydrate and protein combined) of 1:1 and increased gradually to 4:1 depending upon patient tolerance. The patients are then followed up on a three monthly basis during the duration of the KD. The MAKD is initiated as an outpatient by telephone contact between the dietitian and the patient's caregivers with two face to face clinical visits at inception, as well as ongoing reviews on a three monthly basis. Patients and families are reviewed by the dietitian and epilepsy nurse to provide education and counseling regarding food choices and day-to-day aspects of the diet. Medications are changed to tablet formulation prior to starting any KD. Parents are educated on ketone testing and troubleshooting for sick day management, as well as education on the management of hypoglycemia. When patients on either the MAKD or classical KD have difficulty with maintaining ketosis and seizure recurrence, MCT oil may be added to help promote the production of ketosis, as it provides additional ketone per kilocalorie of energy than the long-chain triglycerides that compose the classical KD [5]. The appropriate vitamins and minerals are supplemented in accordance to the international KD guidelines, including oral citrates to reduce the risk of kidney stones. The KD is generally discontinued after 2 years duration, but can be continued in children whose seizures are well controlled and side-effects are low [31].

### Conclusion

This retrospective study suggests that the classical KD and MAKD may provide seizure control and seizure freedom, particularly for those who commit to remaining on the KD out to 24 months. Compliance was related to the efficacy of the KD in terms of seizure reduction, as the children most likely to stay on the diet were those who benefitted most from it.

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