BRIEF COMMUNICATION

Ketonuria and Seizure Control in the Medium Chain Triglyceride and Classic Ketogenic Diets

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ABSTRACT We hypothesized that children receiving medium-chain triglyceride ketogenic diet (MCTKD) experience similar seizure reduction despite lower ketosis compared with classic ketogenic diet (CKD). Children initiating CKD or MCTKD were enrolled in a prospective observational study. Forty-five children completed 6 months of KD (n = 17 MCTKD, n = 28 CKD). The proportion achieving ≥50% seizure reduction was 71% CKD group and 59% MCTKD group; ≥90% reduction was 32% and 36% in CKD and MCTKD groups, respectively. CKD had higher urine ketones (≥8 mmol/L: 79% vs. 36%, p = 0.005). Children receiving MCTKD experience similar seizure control to CKD despite lower urine ketone measures.

RÉSUMÉ : La cétonurie et la diminution du nombre de crises épileptiques par la diète à base de triglycérides à chaîne moyenne et la diète cétogène classique. D'après l'hypothèse des auteurs, les enfants soumis à la diète à base de triglycérides à chaîne moyenne (TCM) connaîtraient une réduction du nombre de crises épileptiques malgré une faible cétose, réduction comparable à celle enregistrée chez les enfants soumis à la diète cétogène classique (DCC). Ainsi, des enfants soumis pour la première fois à la DCC ou à la diète à TCM ont participé à une étude d'observation prospective. Quarante-cinq enfants ont suivi une diète cétogène durant 6 mois (diète à TCM : n = 17; DCC : n = 28). La proportion d'enfants ayant connu une réduction du nombre de crises épileptiques ≥ 50 % était de 71 % dans le groupe de la DCC et de 59 % dans le groupe de la diète à TCM; et la proportion de ceux ayant connu une réduction de ≥ 90 % s'élevait à 32 % et à 36 % dans les groupes de la DCC et de la diète à TCM respectivement. Quant au taux de corps cétoniques dans l'urine, il était plus élevé dans le groupe de la DCC (≥ 8 mmol/L : 79 % contre 36 %; $p = 0{,}005$) que dans l'autre. Enfin, la diminution du nombre de crises épileptiques enregistrées chez les enfants soumis à la diète à TCM était comparable à celle enregistrée chez les enfants soumis à la DCC, et ce, malgré une cétonurie plus faible

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The ketogenic diet (KD) is a high-fat, low-carbohydrate diet, effective in treating medication-resistant epilepsy.[1] Anticonvulsant effects are thought to be due to multiple synergistic mechanisms including increased ketones and reduced blood glucose (BG).[2,3]

The classic ketogenic diet (CKD) and medium-chain triglyceride ketogenic diet (MCTKD) are two types of KDs. CKD is calculated as a ratio of fat to carbohydrate and protein. Long-chain fats are consumed orally or by feeding tube, with total fat intake usually greater than 82% of total daily calories. Prescriptions of CKD may include medium-chain triglyceride (MCT) oil; however, no children on a CKD in this study received MCT oil. Protein is prescribed to meet minimum requirements, and carbohydrate is limited to approximately 3%–5% of total daily caloric intake. MCTKD is a slightly more liberal alternative, allowing for greater carbohydrate and more flexible food choices. It is prescribed as a percentage of macronutrients with total fat intake starting at 71% of total daily caloric intake, 40%–50% from MCT oil. Protein and carbohydrate start at 10% and 19%, respectively, of total daily calories. This diet is administered orally.

The MCTKD and CKD have been shown to have similar efficacy for seizure reduction despite differing macronutrient profiles[4]. The equivalent seizure control of the MCTKD despite lower fat content may be because of the role medium-chain fatty acids (MCFAs) play on the body. Recent studies suggest MCFAs confer anticonvulsant effects: caprylic acid (C8, also known as octanoic acid) and capric acid (C10, also known as decanoic acid) both exerted anticonvulsant effects when administered adjunctively to a normal chow diet in mice.[5,6]

To evaluate the hypothesis that children treated with MCTKD experience similar seizure reduction despite lower urine ketones than children treated with CKD, we evaluated differences in seizure frequency, ketones, BG, weight change, and gastrointestinal (GI) side effects between MCTKD and CKD.

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Children initiating a KD for medication-resistant epilepsy at the Hospital for Sick Children, Toronto, Canada, between September 1, 2013 and November 15, 2017 were invited to enroll in a prospective observational study. Consenting families kept daily seizure and urine ketone diaries. Urine ketones were checked once in the morning and once in the evening. Checking serum beta-hydroxybutyrate (BHB) levels was not routine practice at the time this study was initiated. Children initiated on diet therapy for status epilepticus were excluded.

Per institutional clinical protocol, children are prescribed MCTKD if they are >12 months of age and well-established oral eaters; those who are formula-fed or with small/inconsistent appetites start CKD. Adjustments are made to diet ratio (CKD) or percentage of macronutrient intake (MCTKD) to optimize seizure control and minimize adverse events throughout the course of diet therapy. Adjustments to anticonvulsants during diet titration are typically avoided; however, medical management is at the discretion of the treating team, and medications were altered as needed.

Demographics, anthropometrics, medications, feeding route, and seizure frequency data were collected at diet initiation and 6-month follow-up. At follow-up, additional data collected included percentage of macronutrient intake, fasting BG, and seizure and ketone diaries. Children were classified as having higher ketones if the majority of urine ketones were 8 mmol/L or higher. One participant exclusively measured serum ketones with readings consistently >5 mmol/L which were classified as higher ketones. Z-scores for weight at baseline and follow-up were computed using data from World Health Organization Growth Charts (2007) and Canadian Pediatric Endocrine Group. Differences in weight z-score from baseline to follow-up were calculated by subtracting the z-score at follow-up from baseline z-score. Clinical notes were reviewed for any treatment changes that happened between visits and the presence of an adverse GI event at any point during study, including nausea or vomiting, diarrhea, constipation, or abdominal pain, were summarized by frequency and percent. Diet efficacy was evaluated by comparing the proportion of children with >50% and >90% reduction in monthly seizure frequency to baseline. Data were compared between diet groups.

Tube-fed children represent a distinct cohort of medically complex children and may have more precise adherence to the diet. We conducted a subgroup analysis among oral feeders to determine if feeding method confounds the main study observations.

Fisher's exact test and Wilcoxon rank sum test were used to compare proportions and continuous variables, respectively. Statistical significance was accepted at the 0.05 level, and no adjustments were made for multiple comparisons. Analysis was performed using R (version 3.4.1). Informed consent was obtained from a parent or legal guardian. This study was approved by the Hospital for Sick Children Research Ethics Board.

Sixty-five children were enrolled. Twenty children (10 males; median age 2.4 years) did not reach the 6-month time point: 12 treated with CKD and 8 with MCTKD. One withdrew because seizure records were not maintained, 17 began weaning treatment before 6 months, and 2 died. The two children who died followed a CKD and their deaths were unrelated to the KD.

Forty-five children (28 CKD and 17 MCTKD) were included in this analysis (Table 1). At initiation, children in CKD group were younger ($p = 0.006$) and more likely to be tube-fed ($p < 0.001$). Children in CKD group had a greater monthly burden of seizures at baseline compared to the MCTKD (median 301 vs. 90, $p = 0.003$) and were prescribed a greater number of anticonvulsant medications (median 3 vs. 2, $p < 0.001$).

At six months of diet therapy, there was no significant difference between diet groups in proportion of children achieving ≥ 50% or ≥ 90% seizure reductions (Table 1). Significant differences between groups were noted in ketone measurements, carbohydrate, and fat intake: Children in CKD group were more likely to have higher ketones (79% vs. 36%, $p = 0.005$), lower percent of total calories derived from carbohydrates (median 5% vs. 14%, $p < 0.001$), and higher fat intake (median 86% vs. 77%, $p < 0.001$). There was a trend toward lower fasting BG with CKD: median BG level was 4.1 mmol/L (25th, 75th percentile: 3.5, 4.4) with CKD and 4.4 mmol/L (25th, 75th percentile 4.0, 4.7) with MCTKD ($p = 0.11$).

To remove the effect of feeding method, we examined seizure outcome, BG, and urine ketones among the 24 orally fed children (7 orally fed CKD, 17 MCTKD). There was no significant difference ($p = 0.43$) in BG levels between groups: median BG of CKD group was 4.10 (25th, 75th percentile: 3.58, 4.55) versus 4.40 (25th, 75th percentile: 4.00, 4.65) of MCTKD group. There was a trend toward higher urine ketones (≥8 mmol/L) with CKD compared with MCTKD (86% vs. 35%, $p = 0.07$). There was no significant difference between groups in the proportion of children who experienced ≥50% seizure reduction (59% CKD vs. 71% MCT, $p = 0.67$) or ≥90% seizure reduction (29% CKD vs. 35% MCT, $p > 0.99$).

In this cohort of children with drug-resistant epilepsy, there was no significant difference in the proportion of children achieving ≥50% and ≥90% seizure frequency reduction between CKD and MCTKD. This is consistent with a randomized, controlled trial of MCTKD and CKD which demonstrated 25% of CKD and 19% of MCTKD experienced greater than 50% reduction in seizures at 6 months.[4]

Reduced BG is one hypothesized mechanism of the KD.[2] At 6 months of therapy, 38% of children had BG less than 3.9 mmol/L, at the lower end of the reference range. Comparing diet types, we found a possible trend ($p = 0.11$) toward lower BG in children with CKD. Reduction of BG for seizure control may be more heavily implicated in the CKD than MCTKD; however, further research is necessary to confirm or refute this hypothesis.

Increased hepatic ketone production is another hypothetical mechanism.[2,7] Ketone levels were higher in CKD than MCTKD group. Among orally fed children, the trend was similar. These findings are consistent with a report of lower serum acetoacetate and BHB levels in children on MCTKD than CKD.[4] The relationship between the levels of acetone, acetoacetate, and BHB ketone bodies and seizure control is not well understood.[3,8]

Anticonvulsant benefits conferred by MCTs may explain why the MCTKD diet has similar efficacy despite lower ketosis. Studies have suggested beneficial effects of MCFAs decanoic and caprylic acid.[5,6,9] Caprylic acid exerted an anticonvulsant effect by increasing seizure threshold in mice.[5] Decanoic acid showed an anticonvulsant effect by providing a direct inhibitory effect on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity.[6,9] Decanoic acid is spared in β-oxidation and can accumulate in the brain supporting its ability to act as an anticonvulsant.[10]

This is an observational study with a small number of participants and limited statistical power. The accuracy of seizure

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Table 1: Characteristics of children who reached 6 months on MCTKD or CKD diet therapy

	Overall		MCTKD		CKD		Difference between MCTKD and CKD
N	45		17		28		
Cohort characteristics at diet initiation							
Age, median (25th, 75th %ile)	4.02	1.38, 6.87	5.47	4.03, 8.51	2.21	1.14, 6.57	p = 0.006
Male sex, n (%)	24	53.3	8	47.1	16	57.1	p = 0.55
Tube feed (NG, G-tube, combo tube with oral), n (%)	21	46.7	0	0.0	21	75.0	p < 0.001
Monthly seizure frequency, n (%)							p = 0.003
<10	2	4.4	2	11.8	0	0.0	
10–99	12	26.7	8	47.1	4	14.3	
100–499	16	35.6	4	23.5	12	42.9	
500–1000	10	22.2	2	11.8	8	28.6	
>1000	5	11.1	1	5.9	4	14.3	
Epilepsy etiology[a], n (%)							
Immune	1	2.2	0	0.0	1	3.6	p = 1.00
Structural	9	20.0	2	11.8	7	25.0	p = 0.72
Genetic	25	55.6	11	64.7	14	50.0	p = 0.37
Unknown	12	26.7	5	29.4	7	25.0	p = 0.74
Number of antiepileptic drugs							p < 0.001
0	5	11.1	4	23.5	1	3.6	
1	5	11.1	4	23.5	1	3.6	
2	14	31.1	7	41.2	7	25.0	
3 or more	21	46.7	2	11.8	19	67.9	
Cohort characteristics at ~6-month follow-up							
Percent of daily calories, median (25th, 75th %ile)							
Fat (including MCT oil)	84.5	78.5, 86.6	76.7	72.0, 79.2	86.3	84.0, 88.1	p < 0.001
Protein	8.7	7.8, 10.0	9.0	8.0, 10.0	8.5	7.8, 9.7	p = 0.97
Carbohydrate	6.7	4.5, 14.0	14.3	13.7, 18.2	4.8	3.2, 6.6	p < 0.001
Higher ketones[b], n (%)	28	75.7	6	35.5	22	78.6	p = 0.005
Blood glucose, median (25th, 75th %ile)	4.30	3.80, 4.60	4.40	4.00, 4.65	4.10	3.50, 4.40	p = 0.11[c]
Comparison to baseline seizures, n (%)							
≥50% reduction	30	66.7	10	58.8	20	71.4	p = 0.52
≥90% reduction	15	33.3	6	35.3	9	32.1	p > 0.99
Weight Z-score change, median (25th, 75th %ile)	0.00	−0.36, 0.46	0.01	−0.18, 0.48	−0.01	−0.40, 0.40	p = 0.72[d]
Any GI adverse event reported, n (%)	31	68.9	14	82.4	17	60.7	p = 0.19
Nausea/vomiting	14	31.1	5	29.4	9	32.1	
Abdominal pain	4	8.9	3	17.6	1	3.6	

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Table 1: *(Continued)*

	Overall		MCTKD		CKD		Difference between MCTKD and CKD
Constipation	22	48.9	8	47.1	14	50.0	
Diarrhea	8	17.8	4	23.5	4	14.3	

[a] Categories are not mutually exclusive.
[b] Higher ketones: ≥ 8 mmol/L (urine), ≥5 mmol/L (serum).
[c] Data not available for 6 children (2 MCTKD, 4 CKD).
[d] Data not available for 3 children (2 MCTKD, 1 CKD).

records is a limitation, though likely similar to the challenges faced by similar studies. Participants are not randomly selected for diet type; however, our institution has a consistent selection protocol. Our study examined the relationship between urine ketones and diet type; it is unclear the degree to which these findings may generalize to serum BHB measurements.

This study adds to the limited literature comparing CKD and MCTKD. Children treated with MCTKD experience equivalent seizure reduction to children on CKD despite lower ketonuria.

With increasing evidence for the role of MCT oils in seizure control, this study supports basic research that finds anticonvulsant benefits of MCFAs.

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Conflict of Interest

None.

Statement of Authorship

HL, AK, and ED equally contributed to the conception and design of the research; HL, AK, SA, ET, and ED equally contributed to the acquisition of the data; HL, AK, and ED contributed to the analysis and interpretation of the data. HL, AK, and ED drafted the manuscript. All authors critically revised the manuscript and accuracy of the work and read and approved the final manuscript.

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