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Yield of laboratory testing in pediatric ketogenic diet patients: Critical assessment of abnormal results and impact on clinical care

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ABSTRACT

Objectives: To retrospectively assess the incidence of high beta hydroxybutyrate, low bicarbonate (BIC), high acyl carnitine, low selenium, low magnesium, low zinc, low phosphorus, in a cohort of supplemented patients treated with the ketogenic diet (KD) for medically intractable epilepsy. To analyze effect of age, duration of exposure to KD, type of KD, and route of KD intake on lab abnormalities. To analyze the incidence of clinically actionable results, resulting in medical interventions based on abnormal results and to analyze costs of testing.

Methods: Retrospective chart review and statistical analysis. Association between abnormal values (binary) and categorical variables was tested with Chi-square/Fisher's exact test. Associations between abnormal values (binary) and continuous variables were analyzed with logistic regression. Statistical analyses were performed in SAS 9.4.

Results: We included 91 patients with average duration on diet of 46.73 months (IQR 18.8–75.5 months). Most patients were on the classic KD (81 KD- 59% on 4:1 ratio, 10 modified Atkins diet). 74% were orally fed and 70% completed lab visits to the 12-month mark. There was no significant association between abnormal laboratory parameters and duration of exposure, type of diet, route of administration. Younger children were more likely to have low BIC, high acyl carnitine. Older children were more likely to have low phosphorus. Less than 15% of patients reported clinical changes to suggest dietary deficiency in vitamins/ minerals and in < 11% of cases was an actionable laboratory parameter found.

Significance: Our study is the first to document the real-life incidence of selected tests being abnormal when following consensus guidelines on lab testing. Elimination of tests with low yield will result in cost savings of up to $USD 185 per visit. Low phosphorus is frequently found in patients on KD.

1. Introduction

Epilepsy is refractory to standard pharmacological treatment in 20–30% patients. Ketogenic diet therapy (KDT) is now widely accepted as a viable treatment option for most drug resistant epilepsies and in certain genetic conditions like glucose transporter deficiency and pyruvate dehydrogenase deficiency where it is considered the treatment of first choice (Kelley and Hartman, 2011). The Charlie Foundation commissioned an international committee of neurologists and dietitians with expertise in the ketogenic diet in 2006 with the charge to provide consensus recommendations in the management of the KD. In the absence of any class I evidence these recommendations and a recent 2018 revision are the only published guidelines currently available in the follow up management of patients on KD (Kossoff, 2008; Kossoff et al., 2009a, 2018). These guidelines regarding initiation of the diet, and clinical and laboratory follow-up of patients once the diet is initiated are also adopted by the Child Neurology Society (Kossoff, 2008; Kossoff et al., 2009a, b)

At Children's Hospital Colorado we have offered the ketogenic diet for greater than 15 years. The ketogenic diet clinic is managed by a dedicated registered dietitian and advanced practice provider. All patients are provided recommendations regarding appropriate vitamin and mineral supplements at the outset (pre KD treatment visit) and are seen 1 month after diet initiation and then approximately every 3 months while on treatment with a standard diet duration of 2 years, if effective. Detailed clinical history (focusing on seizure diary;

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complaints of fatigue, perceived weakness, developmental and school progress); examination (focusing on mental exam, tone and strength), and review of systems (focusing on appetite, gastric complaints, skin, hair changes) is performed. Laboratory testing is obtained at baseline to assess safety of implementing the diet and at the time of follow up clinic visits according to a modified protocol from the consensus statement published in 2008 by Kossoff et al. This testing is done to assess the degree of ketosis the patient is in, as well as to study the potential metabolic and nutritional changes caused by this highly restrictive diet. Our post diet initiation (DI) protocol includes 11 laboratory tests (combining both "recommended" and "optional" tests according to the initial consensus guideline) at 4 weeks after diet initiation and then every 3 months for the first 2 years, then every 6 months until diet discontinuation. We test for selenium, phosphorus, zinc, magnesium, complete metabolic panel (includes BIC), complete blood count, vitamin D, carnitine profile (acyl carnitine, total and free carnitine), urinalysis, BHB, urine calcium/creatinine ratio. Fasting lipids are tested every 6 months. Of the above; testing for serum BHB and zinc were considered optional according to the initial international consensus guidelines (Kossoff et al., 2009a, 2018).

2. Rationale

We wanted to analyze the yield of standardized testing protocols for patients on the ketogenic diet specifically by selecting a few laboratory measures from amongst our array of standard tests performed in all patients on the diet- specifically the incidence of high BHB, low BIC, low free and total carnitine, high acyl carnitine, low selenium, low phosphorus, low magnesium, low zinc- in supplemented KD patients; factors associated with abnormal results if any, incidence of clinically actionable results, incidence of actual medical interventions based on abnormal results and costs of testing. We chose to focus this paper on these limited lab values due to due to constraints on resources for the research and the fact that these specific labs have not been systematically looked at although literature is rife with data on changes in lipid profiles after being on the diet -for example.

3. Methods

A retrospective analysis of patients ages 1 year to 18 years who had been on KD for at least 6 months between January 2003 and January 2016 was completed. Institutional IRB approved this study. We used RedCap database housed at the University of Colorado Denver for data analysis(Harris et al., 2009). We collected information for up to the first seven KD clinic follow-up visits (total duration of 2 years on the diet) for each patient starting with visit 1 – which was 1 month after DI. Data collected included date of DI, duration of time on the diet, type of diet: KD vs Modified Atkins diet (MAD), diet prescription (KDT ratio or grams of carbohydrate per day in patients on MAD), type of feeding (oral vs Gtube), and laboratory values for selenium, phosphorus, zinc, magnesium, carnitine profile, BHB, and BIC as available at each visit. We chose to not assess complete blood counts, rest of the serum chemistries and Vitamin D levels due to the possibility of confounding results since many of our patients were also receiving concomitant antiseizure medications which can cause abnormalities in the above values and wanted to keep covariables to a minimum. We also reviewed all clinical documentation specifically for mention of skin, hair, or nail changes (reflecting vitamin and mineral deficiencies), we looked at clinic notes for mention of fatigue, weakness (reflecting possible carnitine deficiency/ phosphorus deficiencies) we looked at clinic notes and telephone calls following clinic or laboratory visits to assess alterations made to diet therapy based on laboratory results and we assessed if the diet provided at least a 50% reduction in seizures at each visit to assess efficacy. We also looked at charges for each of these tests per visit.

Statistical analysis:

Continuous variables were expressed as means [standard deviation] or medians [interquartile range]. Categorical variables were expressed as a percentage. Patients were classified as having abnormal values for a particular result if any were observed between baseline and visit 5 (upto 1 year out since DI- this was done to enhance our numbers). Association between abnormal values (binary) and categorical variables were tested with Chi-square/Fisher's exact test. Associations between abnormal values (binary) and continuous variables were analyzed with logistic regression. Alpha was set to 0.05 for all univariate tests. Statistical analyses were performed in SAS 9.4.

4. Results

We identified a total of 130 patients that were active in our database. Of these, 39 patients were excluded from further analysis because they had not yet completed at least 6 months on the diet or DI was done at another facility and some of the initial data were missing. 91 patients were included in the eventual analysis. Of these, 87 (95.60%) were still on the diet and 4 had completed treatment at time of analysis. Average duration on diet was 46.73 months (IQR 18.8–75.5 months). 81 patients were on the ketogenic diet while 10 were on MAD. Of patients on the ketogenic diet 48 were on a 4:1 ratio (59.26%) while 22 (27%) were on a 3:5:1 ratio. 5 (50%) patients on the MAD were receiving 10 g or less of carbohydrate per day. 74.72% (68/91) patients were orally fed while 39.56% were fed via G tube and 13 patients were fed via both routes. 66/91 (72.52%) patients had completed some or all laboratory visits to the 12-month mark. All laboratory results are detailed in Table 1 below. Mean age of our population was 5.3 years (SD 4.0; range: 0.6–18); for patients on MAD mean age was 9.7 years (SD-4.9 range: 3.8–17); Mean age on KD was 4.7 years (SD 3.5;range:0.6–18) (Table 2).

For patients with available data, 90 out of 90 (100.00%) had an instance of high BHB, 60 out of 91 (67%) had an instance of low BIC; 74 out of 88 (84.09%) had an instance of high acyl carnitine, 73 out of 89 (82.02%) had an instance of low free carnitine, 25 out of 90 (27.78%) had an instance of low total carnitine, 3 out of 85 (3.53%) had an instance of low magnesium, 14 out of 87 (16.09%) had an instance of low selenium, 11 out of 87 (12.6%) had an instance of low zinc and 39 out of 90 (43.33%) had an instance of low phosphorous.

The KD diet was significantly more likely to exhibit low BIC (70.37% vs 30%, $p = 0.03$) and high acyl carnitine (89.74% vs 40.00%, $p = 0.0008$) when compared to the MAD. G tube fed patients, as opposed to orally fed patients, were significantly more likely to exhibit high acyl carnitine (94.29% vs 77.36%, $p = 0.03$), and less likely to exhibit low free carnitine (5.71% vs 41.82%, $p = 0.0002$). Except for low free carnitine level, the odds of which increased with longer baseline diet duration (Odds ratio per month = 7.41, $p = 0.009$), there was no statistically significant association between any abnormal results and duration of diet exposure; meaning that patients who were exposed for 12 months were not more likely to have a laboratory abnormality compared to those who were exposed for lesser duration (Table 3). Increasing baseline age was significantly associated with decreased odds of low BIC (odds ratio per year = 0.799, $p = 0.0002$) and high acyl carnitine (odd ratio per year = 0.754, $p < 0.0001$), and with increased odds of low phosphorus (odds ratio per year = 1.22, $p = 0.0009$).

In reviewing the clinical documentation at each visit, 13 patients in the total sample (14.3%) reported skin, hair, and/or nail changes. Of these, only two patients had a low magnesium, selenium, or zinc level at the corresponding visit. Two patients reported a rash (not further described in the clinical chart) -one was found to have low levels of both selenium and zinc at that visit. The second patient had a low selenium. In all other reports of changes to skin, hair, or nails, where available, the patients had normal magnesium, selenium, or zinc levels. Thus, it was rare that a reported symptom of hair, skin, or nail change was correlated with a mineral deficiency that could cause these

Table 1
All laboratory data from 91 patients.

	Visit 1 1 month	Visit 2: 3 months	Visit 3: 6 months	Visit 4: 9 months	Visit 5: 12 months	Visit 6: 15-18 months	Visit 7: 2 years
# of patients with some or all labs by visit	91	86	82	69	66	56	47
Normal BHB	0.02-0.27 mmol/L						
Average BHB (IQR 25%-75%)	4.59 (2.6-6.4)	4.5 (2.9-5.9)	4.16 (2.3-5.6)	4.38 (3-6.08)	4.27 (3.26-5.5)	4.43 (2.99-6.11)	4.04 (2.8-5.86)
High BHB	83/84 (99%)	81/82 (98%)	78/81 (96%)	63/65 (97%)	62/63 (98%)	49/51 (96%)	40/44 (91%)
Normal BIC	20-31 mmol/L						
Average BIC(IQR)	20.55 (18-23)	21.13 (19-24)	20.73 (19-23)	21 (20-23)	21.32 (19-23)	21.42 (20-23)	22.09 (20-24)
Low BIC	32/89 (36%)	26/86 (30%)	28/82 (34%)	15/67 (22%)	20/65 (31%)	10/53 (19%)	8/47 (17%)
Normal Total Carnitine	35-84 nmol/mL						
Average Total Carnitine (IQR)	52.28 (40-64)	67.5 (47-83)	69.84 (49-86.25)	72.45 (50-85)	73.20 (54-88)	68.37 (50.75-84)	71.58 (54-84)
low Total Carnitine	17/86 (20%)	5/82 (6%)	6/77 (8%)	1/67 (1%)	1/65 (2%)	3/52 (6%)	1/45 (2%)
Normal Free Carnitine	24-63 nmol/mL						
Average Free Carnitine (IQR)	22.65 (15-29.8)	28.91 (19.2-34)	29.9(23-34	30.46 (23-38)	31.31 (26.75-35.5)	29.87 (23-34)	33.39 (24.25-38.75)
low Free Carnitine	50/86 (58%)	34/82 (41%)	21/77 (27%)	18/67 (27%)	14/64 (22%)	18/52 (35%)	10/46 (22%)
Normal Acyl Carnitine	4-28 nmol/mL						
Average acyl carnitine(IQR)	29.85 (19-36)	39.20 (11-52)	40.31 (27-52)	41.99 (26.5-53.5)	42.73 30.8-53.2)	38.03 (26-49)	38.76 (29-46)
High Acyl Carnitine	41/84 (49%)	44/70 (63%)	55/75 (73%)	48/67 (72%)	52/64 (81%)	36/51 (71%)	35/46 (76%)
Normal Selenium	70-150 ng/mL						
Average Selenium(IQR)	107.32 (89-108)	96.23 (87-108)	100.32 (86-107)	97.88 (84.5-107)	96.75 (86.75-105.25)	101.29 (85-109)	97.43 (87.75-105.5)
Low Selenium	3/81 (4%)	3/78 (4%)	5/75 (7%)	2/59 (3%)	5/60 (8%)	3/49 (6%)	4/44 (9%)
Normal Zinc	0.6-1.2 mcg/mL						
Average Zinc (IQR)	0.82 (0.71-0.94)	0.89 (0.71-1)	0.9 (0.78-0.99)	0.87 (0.77-0.91)	0.88 (0.73-0.97)	0.86 (0.75-0.96)	0.86 (0.74-0.99)
Low Zinc	8/82 (10%)	2/76 (3%)	1/73 (1%)	1/59 (2%)	2/59 (3%)	1/46 (2%)	1/45 (2%)
Normal Magnesium	1.6-2.3 mg/dL						
Average Magnesium(IQR)	2.02 (1.8-2.2)	2.28 (1.9-2.2)	1.96 (1.8-2.1)	1.95 (1.8-2.1)	1.94 (1.8-2.1)	1.95 (1.8-2.1)	1.94 (1.8-2.1)
Low Magnesium	1/70 (1%)	0/72 (0%)	1/70 (1%)	2/56 (4%)	1/60 (2%)	0/48 (0%)	1/43 (2%)
Normal Phosphorus	4.5-5.5 mg/dL						
Average Phosphorus (IQR)	4.92 (4.6-5.3)	5.07 (4.6-5.6)	5.02 (4.6-5.4)	4.88 (4.5-5.4)	4.92 (4.5-5.4)	4.89 (4.6-5.1)	4.94 (4.7-5.5)
Low Phosphorus	13/77 (17%)	14/78 (18%)	16/77 (21%)	15/61 (25%)	15/65 (23%)	6/50 (12%)	9/45 (20%)

BHB: Beta hydroxybutyrate; IQR: Interquartile Range; BIC: Bicarbonate.

symptoms. We did not see an association between any particular ketone levels and seizure reduction, meaning no one particular BHB level had a greater likelihood of resulting in greater than 50% seizure reduction.

5. Discussion

sThe ketogenic diet is a valuable asset in the treatment of medically intractable epilepsy with radical and diffuse effects on the metabolism of every cell in the body due to its classic composition of 80–90 percent fat with approximately 5–7 percent protein and 3 percent carbohydrate (Bergqvist, 2012; Zupec-Kania and Zupanc, 2008). This diet lacks vitamins, trace minerals and electrolytes and needs to be properly supplemented (Neal et al., 2012). Prescribing such a diet for a long period therefore warrants monitoring of laboratory parameters (labs) to evaluate- among other things- degree of ketosis, electrolyte abnormalities and deficits in vitamins, minerals and trace elements. It is felt that the

Table 2
Percentage of patients with abnormally flagged laboratory tests and corrections made at any visit- this table also includes cost of the stated test.

	BHB	BIC	Total carnitine	Free carnitine	Acyl- carnitine	Selenium	Zinc	Mg	Phos
Normal	0.02-0.27 mmol/L	20-31 mmol/L	35-84 nmol/mL	24-63 nmol/mL	4-28 nmol/mL	70-150 ng/mL	0.6-1.2 mcg/mL	1.6-2.3 mg/dL	4.5-5.5 mg/dL
% Abnormal	100%	67%	27.8%	82%	84%	16%	12.6%	3.5%	43.3%
% times changes made for abn results	2.1%	10.8%	1.5%	14%	0.6%	2.3%	1%	0.7%	1.3%
Cost of test	$220	$218 (for CMP)	$224 (for carnitine profile)	$224 (for carnitine profile)	$224 (for carnitine profile)	$199	$112	$96	$88

BHB: Beta hydroxybutyrate; BIC: Bicarbonate; Mg: Magnesium; Phos: Phosphorus.

Table 3
Association of age, type of feeding, type of diet and duration of exposure on incidence of laboratory abnormalities.

Laboratory parameter	Age (OR, 95% CI, p value)	G tube fed (OR, 95% CI, p value)	Type of diet Ketogenic (OR, 95% CI, p value)	Duration on diet (OR, 95% CI, p value)
Low BIC	1.241	2.000	5.541	1.238
	(0.701, 0.909)	(0.729, 5.756)	(1.123, 35.248)	(0.686, 2.661)
	0.0003	0.1399	**0.0281**	0.5008
High Acyl carnitine	0.756	4.829	13.125	1.015
	(0.637, 0.872)	(0.956, 46.731)	(2.400, 74.383)	(0.511, 2.768)
	< **0.0001**	0.0336	**0.0008**	0.9707
Low free carnitine	1.190	0.430	0.474	7.405
	(1.004, 1.483)	(0.122, 1.485)	(0.010, 3.939)	(1.472, 57.340)
	0.0443	0.1260	0.6828	0.0091
Low total carnitine	1.103	0.084	0.208	0.912
	(0.986, 1.239)	(0.009, 0.396)	(0.040, 1.001)	(0.402, 1.701)
	0.0858	**0.0002**	0.0250	0.7863
Low magnesium	0.969	0.781	–	0.624
	(0.647, 1.251)	(0.013, 15.63)	(0.415, -)	(0.025, 2.501)
	0.8362	1.0000	1.0000	0.6595
Low selenium	0.900	1.278	1.828	0.842
	(0.735, 1.053)	(0.327, 4.714)	(0.216, 86.208)	(0.263, 1.761)
	0.2059	0.6784	1.0000	0.6924
Low phosphorus	1.204	0.800	0.286	0.946
	(1.070, 1.379)	(0.308, 2.052)	0.045, 1.385)	(0.497, 1.701)
	0.0014	0.6107	0.0947	0.8507
Low zinc	0.938	2.178	–	1.645
	(0.763, 1.102)	(0.497, 9.842)	(0.415, -)	(0.807, 3.320)
	0.4677	0.3196	0.349	0.1548

BIC: Bicarbonate, - in the column on effect of type of diet is due to low levels of patients on MAD where an odds ratio or upper limits of CI tended to infinity and therefore not applicable.

majority of these deficits will be found after at least 3 months of exposure to ketogenic diet (Bergqvist, 2012).

The international ketogenic diet consensus statement regarding monitoring and several other papers since that time recommend monitoring of labs every 3–6 months. There is no previously published data that reports the incidence of lab abnormalities in supplemented children. Most published data with over 50 patients focus on efficacy of the diet or lipid profile changes in the short and long-term (Hemingway et al., 2001; Patel et al., 2010). We have a high retention rate in our ketogenic diet clinic [87 patients were still on the diet with an average duration of 47 months of exposure [retention rate greater than 95% at 2 years] and therefore a unique capacity to look at the incidence of laboratory abnormalities over this time. Additionally, in our cohort; majority of the patients (86%) were on a higher than 3.5:1 ratio thus increasing the chances of finding such abnormalities. Our objective was to assess the real-life incidence of these abnormalities, factors associated with finding them and assessing how many times corrections had to be made to diet and/or supplementation based on the above abnormalities. We also wanted to perform a cost analysis of laboratory testing every 3 months. In this enriched cohort of patients, the highest incidence of abnormality was in the BHB value. This is to be expected given the fact that the ketogenic diet forces the body into a state of compensated metabolic acidosis (Bergqvist, 2012). Although BHB is not a “recommended” lab test per the original guidelines, we use it at our centre for assessment of degree of ketosis to “fine tune” the diet and as a mark of compliance.

With exposure to a high fat diet, carnitine profile was the next common abnormality. We do not routinely supplement patients with carnitine unless deficiencies are noted, with the exception of concurrent use of valproic acid. We had hoped to analyze the BHB level and carnitine metabolites initially to look for association between efficacy of diet (> 50% seizure reduction) and degree of ketosis (high acyl carnitine is a surrogate for ketosis). There was no clear association between a particular value of BHB or any portion of the carnitine profile and efficacy. Similar results have been published elsewhere (Carmant, 2008; Schoeler et al., 2017, 2013).

Amongst minerals, phosphorus was most likely to be low in our cohort. All patients are supplemented with a multivitamin and calcium/vitamin D at a minimum. Many over-the-counter multivitamins either do not contain phosphorus, or contain very little phosphorus. Multivitamins such as NanoVM™ recently became eligible for coverage by Medicaid and available from Durable Medical Equipment companies in Colorado. However, for various reasons (patient does not have Medicaid, the complete multivitamin is not tolerated, the patient was started on diet before the complete multivitamin was readily available) many patients remain on an over-the counter multivitamin with minimal phosphorus content, if any. This could explain the higher incidence of low phosphorus levels in our population.

The incidence of abnormalities in selenium, magnesium and zinc in our supplemented cohort was less than 17%. Similar results were published in other, smaller series of patients with a shorter duration of follow-up(Chesney et al., 1999; Hayashi et al., 2013). Although small case series reporting selenium and other mineral deficits have been published(Bergqvist et al., 2003; Hayashi et al., 2013; Kirby and Danner, 2009; Sirikonda et al., 2012), the actual incidence of finding such deficits over a chronic exposure of 2 years is not available.

At Childrens Hospital Colorado, we have historically not always measured all of the above tested laboratory variables at baseline before DI and therefore could not determine degree of drop in levels of these micronutrients over time. None of the resulting levels were < 2 times lower limit of normal however and similar findings have been published by Christodoulides etal.(Christodoulides et al., 2012). This may suggest that rapid decreases in micronutrient levels as described by Sirikonda et al (Sirikonda et al., 2012) while on the ketogenic diet are rare.

The timing of when the laboratory abnormalities were found had no relationship to duration of exposure to the diet. We were just as likely to find an abnormally low value of selenium in the first visit as in the seventh visit at the end of 2 years on the diet for example. Similar findings have been found in other studies(Bergqvist et al., 2003; Sirikonda et al., 2012). Why this happens is unknown although we could speculate that this is due to non-compliance regarding supplementation. It was not possibile to assess nutrient intake retrospectively in this data analysis.

In our study we found that patients with a low phosphorus were older than patients with a normal phosphorus. The inverse was true of

low BIC and high acyl-carnitine levels i.e younger patients tended to have more abnormal levels. The Adequate Intake (AI) level of phosphorus in children 6–12 months of age is 275 mg daily. The Recommended Daily Allowance (RDA) of phosphorus in children 9–18 years of age is 1250 mg daily. Since many over-the counter multivitamins contain little to no phosphorus and needs for this mineral drastically increase with age, it is possible that this level is more frequently abnormal in older patients since they are receiving even less of the DRI over time as they age.

Majority of children on KD reviewed in this cohort were on a higher ratio (4:1 or 3.5:1). Theoretically, young children have higher energy needs and, therefore, they produce ketones more easily than older children and adults. The increased frequency of high BHB and low bicarbonate levels in young children could be because they were on the same high ratio as the older children, but produced ketones more efficiently causing frequent acidosis.(Lamers et al., 1985)

The cost to do all the selected laboratory tests in our study was USD $1760. We realize that this cost data is restricted and only reflective of our hospital protocol. If for example, we decreased phosphorus and magnesium testing to every 6 months as opposed to every three months it would result in a total savings of USD $185 per visit. Our clinic sees approximately 10 patients per week. Over the course of a year, this could be a savings of USD $96,200 for all patients

Limitations of our study:

We are limited by the retrospective nature of our analysis. We did not have baseline values on all our patients (before diet initiation) and therefore can only comment on the lab values at 1 month after DI and thereafter. We specifically chose to analyze only certain laboratory abnormalities amongst others tested in our protocol. Our hospital protocol combines both the recommended and optional tests mentioned in the original consensus guidelines and additionally we also test for BHB at every visit. To eliminate confounders of high altitude in Colorado (affecting red blood cell counts and hematocrit) and several concomitant antiseizure medications that are variably prescribed to our patients we did not analyze complete blood count, serum chemistries (other than BIC) and vitamin D levels as part of this research. We chose not to look at lipids in this paper, as there are several papers that address this already. We are also limited in estimating adherence to the diet and adherence to supplements. However, considering that high BHB level was the most frequent laboratory abnormality in this cohort-we think that KD adherence was not a major limitation of our study. Despite the presence of a protocolized laboratory order set not every laboratory test was completed for each patient per visit. This could have been because of insufficient quantity of blood drawn, difficult sticks, or patient non-compliance. Not all patients in our analysis started the diet at the same time and thus the eventual duration of exposure is not the same for every patient, but since we use a standardized protocol they were all equally likely to have similar chance of abnormalities. Additionally, our cohort is highly enriched for patients on KD and only 10 patients are on MAD. Hence the association of patients getting more ketotic on KD versus MAD could be confounded by the factor of age as MAD patients are older.

Conclusion: KD is a well-accepted treatment for intractable epilepsy. Many laboratory tests done at follow up visits are abnormal as this treatment affects the metabolism of both macro- and micronutrients. In our cohort, there was no clear correlation between abnormal laboratory results and duration of exposure to the diet. Age seems to modify the chance of having abnormal results. Younger children may be at greater risk for acidosis as they produce ketones more efficiently than older children. Over the years some of the initial KD related guidelines were modified to allow inclusion of centers with limited means for initiation and management of the diet(Kossoff et al., 2015) This publication recommends that resource poor centers eliminate testing for selenium, magnesium, phosphorus. Our data shows that the incidences of abnormalities, specifically in selenium, zinc, and magnesium, are indeed low providing further evidence to support this recent recommendation to check these labs less frequently. Universal supplementation with a multivitamin product that contains trace minerals maybe the reason that incidence of laboratory abnormalities was as low as we found in our cohort.

In an increasingly cost-conscious health care society; whether it is a high income or a low-income country, we cannot forget the financial burden of frequent laboratory tests to families and our health care system. We are not suggesting that abnormal laboratory values (selenium for example) aren't concerning and we suggest close monitoring in the few that they occur in. More data from other ketogenic centers across the country will be needed to further streamline the current recommendations for laboratory testing in developed countries but our paper takes the first step in that direction.

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