Supplementary Appendix

DIET Trial

Contents

Efficacy of Ketogenic Diet, Modified Atkins Diet and Low Glycemic Index Therapy Diet Among Children with Drug Resistant Epilepsy: A Randomised Non-Inferiority Trial

INTRODUCTION

Epilepsy is a common treatable condition with a lifetime risk of one to three percent(1). The incidence of epilepsy in children ranges from 0.5-1%(2, 3). Anti-epileptic drugs (AEDs) are the primary drugs for treatment of epilepsies across all age groups and are effective in controlling seizures. However, approximately one-third of patients will not respond to pharmacological management and will require interventions via other modalities(4). The seizures per se, especially when they are refractory, are disabling and can negatively impact psychological and social functioning of the child and family(3). Also these drug resistant epilepsies are more commonly associated with developmental delay, psychological disorders including attention deficit hyperactivity disorder, learning disabilities, depression and anxiety(3). In addition, AEDs especially when used as polytherapy are commonly associated with adverse events like sedation, cognitive impairment and drug interactions. Among the non-pharmacological therapies, epilepsy surgery, vagus nerve stimulation and dietary therapies are the viable options. Epilepsy surgery and vagal nerve stimulation involve special expertise that is available only in few centres in India. Also, both these options are expensive and are beyond the financial scope of many patients. In addition, many patients are not optimal candidates for epilepsy surgery and further more decline surgery due to risk of intolerable motor, language, or memory deficits. In view of the aforementioned, dietary therapy is a more attainable goal for these children with drug resistant epilepsy.

Nearly a century ago, fasting was first recognised as an effective means to control seizures(5, 6). Fasting had inherent limitations for universal application for epilepsy treatment. Hence, in 1921 Wilder suggested that diet high in fat and low in carbohydrate might mimic the ketotic effect of fasting. Wilder reported that half of his patients at the Mayo Clinic had significant seizure control on this ketogenic diet (KD)(7). This was further substantiated by Peterman who reported substantial improvement in a group of 37 patients when treated by the diet(8). KD is a medically supervised high fat, low carbohydrate and restricted protein diet. This has been shown to be effective in retrospective and prospective observational studies as well as in randomised controlled trials, with more than half of children who were treated showed a greater than 50%

reduction in seizures, and many were seizure free after only 3 months(9-12). However, KD has its drawbacks. It requires rigorous weighing of food items and is tedious to prepare and administer. Some children find KD to be too restrictive and many other find it unpalatable. Also, KD may be associated with renal stones, constipation, acidosis, diminished growth, weight loss, and hyperlipidemia(9, 10, 13, 14). Thus, effective alternative dietary therapies for epilepsy are needed.

As the restrictiveness of KD was challenged, two alternative dietary therapies were created at Johns Hopkins in 2003, and at Massachusetts General Hospital in 2005. These therapies were Modified Atkins Diet (MAD) and Low Glycemic Index diet Treatment (LGIT) respectively. Robert C Atkins first initiated a dietary regimen for weight loss, that became popular as Atkins diet. In 2003, a modification of this dietary scheme was found to be effective in controlling seizures among six children(15). In 2006, the diet was first formally referred to as the "Modified Atkins Diet" (MAD) to distinguish it from the Atkins diet(16). Over the last decade, several prospective and randomised trials have demonstrated MAD to be better than standard AEDs for controlling seizure among children with drug resistant epilepsy(16-20). The advantages of the MAD include a more liberal carbohydrate and unrestricted protein intake, so that growth will not suffer. Another special advantage of the MAD especially in resource-poor settings is that it is much simpler to explain to parents and administer.

Carbohydrate intake rapidly terminates the protective effects of fasting and KD(21). Serum glucose levels have been positively correlated with seizure susceptibility in animal models(22, 23). Based on these observations, it has been thought that a tight glycemic control may be beneficial in terms of lower seizure susceptibility. Low glycemic index diet treatment (LGIT) has been designed with this principle in mind(24, 25). Limited literature has reported LGIT to be efficacious among children with drug resistant epilepsy (24-26).

Limited studies have demonstrated that MAD and LGIT are efficacious in reducing seizure frequency among children with drug resistant epilepsy. A few prospective and randomised studies have compared MAD and LGIT with KD, but the data is scarce and lacks substantial evidence(16-20, 24-27). Hence this randomised trial is undertaken to assess whether MAD or LGIT are non-inferior to KD with regard to seizure control at twenty-four weeks among children with drug resistant epilepsy.

HYPOTHESIS

In 1-15 year old children with drug resistant epilepsy, use of Modified Atkins Diet or Low Glycemic Index Therapy as an add on to the ongoing anti-epileptic drugs would not be inferior to ketogenic diet by >15% in terms of seizure reduction from baseline seizure frequency at 24 weeks

RESEARCH QUESTION

In children between 1 year and 15 years with drug resistant epilepsy, is the use of Modified Atkins Diet or Low Glycemic Index Therapy as an add on to the ongoing anti-epileptic drugs non-inferior to ketogenic diet by >15% in terms of seizure reduction from baseline seizure frequency at 24 weeks?

STUDY OBJECTIVES

Aim of the study

To devise an optimal dietary therapy for management of drug resistant epilepsy in children and adolescents

Primary objective

- Compare MAD, LGIT, and KD for seizure reduction in drug resistant epilepsy following 24 weeks of dietary therapy in 1-15 year old children on anti-epileptic drugs

Secondary objectives

- Determine efficacy of MAD as compared to LGIT for seizure reduction in drug resistant epilepsy following 24 weeks of dietary therapy in 1-15 year old children on anti-epileptic drugs
- Determine proportion of patients who achieve > 50% seizure reduction from baseline after 24 weeks in each of the three dietary arms
- Evaluate effect of each dietary therapy on behaviour and cognition in these children
- Estimate the nature and frequency of adverse events in the three study arms
- Estimate blood levels of polyunsaturated fatty acids levels in each arm and correlate it with change in seizure frequency

MATERIALS AND METHODS

Study design

This will be a non-inferiority randomised controlled study with three parallel arms (KD, MAD, and LGIT).

Randomisation technique

Variable block size randomisation (3, 6 or 9) method using computer generated randomisation sequence will be used. This will be done by personnel who would not be involved in patient care.

Allocation concealment

Serially numbered sealed opaque envelopes containing randomisation group codes will be prepared by personnel not involved in the conduct of study. Each envelope would be opened according to their serial number at the time of randomisation and the patient will be allocated to his/her respective treatment groups.

Study period

The study will be conducted over 16 months from April 2016 to Aug 2017.

Ethical clearance and trial registration

These dietary therapies are being used in clinical fields for control of drug resistant epilepsy for more than two decades. The safety of these dietary therapies is well established. The trial aims at determining the non-inferiority of LGIT or MAD as against KD. The study has been approved by the Institute Ethics Committee vide letter no IECPG/218/24.02.2016 dated 8th April 2016. The trial has been registered at clinicaltrials.gov vide ClinicalTrials.gov ID: NCT02708030. Written informed consent will be obtained from the parents.

During the conduct of the study, the patients will not be subjected to any extra hospital visits or any additional phlebotomy. The hospital visits during the trial would be the routine visits accompanying

the dietary therapy. All the investigations (except blood PUFA levels, mentioned later) are part of standard of care during dietary therapy in epilepsy. The blood samples for PUFA estimation will be drawn at baseline and at 24 weeks during the venipuncture for routine investigations. The study will be conducted according to the principles of Good Clinical Practice (GCP) and declaration of Helsinki.

Study set up and selection of patients

Patients with drug resistant epilepsy presenting to the Pediatric Outpatient Department and Pediatric Neurology Clinic, Department of Pediatrics All India Institute of Medical Sciences, New Delhi, would be assessed for eligibility.

Inclusion criteria

1. Children aged 1-15 years with drug resistant epilepsy (drug resistant epilepsy for the study will be defined as seizure frequency >4 seizures per month, and treatment failure of ≥2 prescribed anti-epileptic drugs in the maximum tolerated doses; For west syndrome, drug resistant epilepsy will be defined as >4 cluster of spasms per month despite treatment with anti-epileptic drugs and either ACTH or vigabatrin). Drug levels will not be done to ascertain DRE.
2. Willing to come for regular follow up

Exclusion criteria

1. Surgically remediable cause for drug resistant epilepsy. Epilepsy would be deemed surgically remediable if there is a surgically resectable lesion including mesial temporal lobe epilepsy, neo-cortical epilepsy, lesional epilepsy including primary brain tumors (ganglioglioma, dysembryoplastic neuroepithelial tumors), vascular malformations and malformation of cortical development (focal cortical dysplasia, hemimegalencephaly).
2. Proven inborn error of metabolism except those in which KD is indicated (i.e., Pyruvate dehydrogenase deficiency and GLUT-1 Deficiency); explained below.
3. Previously received KD, MAD or LGIT
4. Known case of

a) Chronic kidney disease

b) Chronic liver disease/ GI illness

c) Chronic heart disease (congenital and acquired)

d) Chronic respiratory illness

All children with DRE, initially will undergo clinical evaluation and neuroimaging. If neuroimaging is suggestive of surgically remediable epilepsy, the child would be referred for pre-surgical evaluation and excluded from the study. If no underlying etiology could be discerned, then metabolic testing (arterial lactate, urine for reducing substances, tandem mass spectrometry, urinary gas chromatography mass spectrometry, serum biotinidase levels, CSF lactate, CSF glucose and CSF: serum glycine) would be performed. For the subset of patients, with no identifiably cause of DRE or with clinical/ metabolic/ neuroimaging features suggestive of genetic etiology, targeted next generation sequencing would be performed. Children with features suggestive of IEM on any of aforementioned assessment would be excluded from the study. In addition, children who have previously been treated with KD, MAD, or LGIT would also be excluded. Families and caregivers will be made to understand the implications of diet, need to bring the child to trial center, and requirement for regular home monitoring for ketosis, through personal interviews and a patient information sheet.

Intervention

Eligible patients will be randomized to receive either MAD along with the ongoing anti-epileptic medications, or LGIT with ongoing anti epileptic medications, or KD with ongoing anti-epileptic medications.

Outcome variables

Primary outcome variable

Objective	Outcome Variable	Definition of Outcome Variable	Method of Measurement
Efficacy of MAD as compared to KD and LGIT as compared to KD for seizure reduction in drug resistant epilepsy following 24 weeks of dietary therapy in 1-15 year old children on anti-epileptic drugs	Change in seizure frequency	Percentage of seizure reduction from baseline at 24 weeks*	Daily seizure log maintained by parents^

*Percentage Seizure Reduction at 24 weeks = $\frac{y-x}{x} \times 100$

y= Mean daily seizures at 24 weeks as measured over past 4 weeks
x= Mean daily seizures at baseline as measured over past 4 weeks

^Seizure log contained details of number, duration and types of seizures as recorded by parents

Secondary outcome variables

Objective	Outcome		Method of Measurement
Efficacy of MAD as compared to LGIT for seizure reduction in drug resistant epilepsy following 24 weeks of dietary therapy in 1-15 year old children on anti-epileptic drugs	Change in seizure frequency	Percentage of seizure reduction from baseline at 24 weeks*	Daily seizure log maintained by parents, which recorded number, duration and types of seizures
Proportion of patients who achieve >50% seizure reduction from baseline at 24 weeks after diet initiation	Number of patients with > 50% seizure reduction in each dietary arm	Proportion of patients with > 50% seizure reduction	Daily seizure log maintained by parents, which recorded number, duration and types of seizures
Evaluate effect of each dietary therapy on behavior and cognition in these children	Change in SQ and behavior with each dietary therapies	- Percentage change in SQ at 12 and 24 weeks as compared to baseline - Percentage change in CBCL scores for each domain at 12 and 24 weeks vis-à-vis baseline	- IQ will be measured using VSMS at baseline, 12 and 24 weeks - Behavior assessment will be done using CBCL at baseline, 12 weeks, and 24 weeks

Evaluate adverse events - Vomiting - Constipation - Diarrhoea - Weight loss - Renal calculi - Dyslipidemia	Proportion of patients with adverse events in both groups	Occurrence of each adverse event	- Adverse events vomiting, constipation and diarrhoea were checked by parents record - Weight will be monitored by electronic weighing scale every month - Lipid profile will be checked by analysis of fasting serum sample at 12 weeks and 24 weeks - Calcium creatinine ratio will be checked by spot Urinary Calcium/Creatinine analysis at 12 and 24 weeks
Evaluate ω-3 polyunsaturated fatty acid levels and correlate it with change in seizure frequency	Correlate seizure frequency change at 6 months with ω-3 polyunsaturated fatty acid levels	Percentage change in ω-3 polyunsaturated fatty acid levels compared to percentage change in seizure frequency	Measurement of ω-3 polyunsaturated fatty acid levels

*Percentage Seizure Reduction at 24 weeks = $\frac{y-x}{x} \times 100$

y= Mean daily seizures at 24 weeks as measured over past 4 weeks
x= Mean daily seizures at baseline as measured over past 4 weeks

Sample size estimation

This trial is designed to demonstrate non-inferiority of MAD and LGIT as compared to KD among children with drug resistant epilepsy. The predetermined non-inferiority margin δ has been assumed to be an absolute 15% difference between the treatment arms. Assuming a two-sided α of 0·05, a power of 80%, and standard deviation of 30% among treatment outcome after 24 weeks of treatment 50 patients per group were needed. Assuming a 10% dropout rate, the required sample size is 165 patients (55 in each study arm).

The non-inferiority margin of 15% has been set only for the primary endpoint. This limit has been chosen in accordance with ILAE stipulation of lower limit of 95% confidence interval to be above a 20% lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per-protocol study population. Though this guideline is primarily for efficacy of AED as

initial mono therapy, in absence of other guidelines, the same has been used to keep the non-inferiority margin of 15 (i.e., below 20%). Based on this, MAD and LGIT efficacy to control seizures will be judged non-inferior to KD when the lower limit of the 95% CI of the treatment difference is above –15%. The standard deviation of 30% between treatment arms has been chosen based on our previous unpublished work comparing seizure reduction between MAD and KD at 6 months.

Procedure

All children attending the Pediatric Neurology OPD and Pediatric Neurology Clinic at Child Neurology Division, Department of Pediatrics, AIIMS will be screened for drug resistant epilepsy. After fulfillment of inclusion and exclusion criteria, written informed consent will obtained from the parent or the legal guardian. Thereafter the parents/ guardians will be shown a presentation depicting various types of seizure semiology to aid them in recognizing these seizure among their children.

Subsequently there will be a run in period of 4 weeks during which each child will undergo a detailed detailed clinical evaluation according to a structured proforma, and baseline investigations. The parents will be advised to maintain a seizure record during this period to record the frequency of baseline seizures. Seizure type, frequency, age at onset, perinatal details, family history, developmental status and treatment history will be recorded. Corticosteroids or ACTH (if patient is already on) will be tapered off two weeks before starting diet. All the medications will be changed to carbohydrate free preparations, wherever available. No changes will made to the patients' antiepileptic medication during the four week baseline or the 6 month study periods, unless medically indicated; e.g. drug side effects, or status epilepticus; in which case appropriate changes

will be made to their medications. The details of baseline investigations have been illustrated in figure 2.

Following the run in period of 4 weeks, the patients will be randomized to the MAD or LGIT or KD arm. The patients in KD arm will be admitted to the hospital for initiation of diet. MAD and LGIT will

be initiated on out patient basis. The standard procedures for diet initiation will be followed. The diet plan of each child will be discussed individually with the parent. The staple diet of the family vegetarian/ non-vegetarian status, specific food aversions or liking that the child has, would be comprehended before deciding the diet menu. In addition, they would be advised about the food replacements to void monotony of food. Sample menu of each of the three diets has been attached as Appendix A.

Follow up

Outpatient Followup

Patients will be followed up as outpatients at 4 weeks, 12 weeks and 24 weeks after initiation of dietary therapy. A dietary intake diary that will be documented by the parents will be reviewed at each visit to compute calorie and carbohydrate intake. This will be used to evaluate and reinforce compliance with the prescribed diet. Also, parents will be instructed to maintain a log of daily urinary ketones (as measured by urinary ketosticks). The urinary ketones will be a surrogate marker of ketosis achieved during dietary therapy.

Seizure frequency will be assessed using seizure log which will be maintained by the parents. During each visit, the number of seizures in the previous weeks will be counted and documented. Body weight will checked using electronic weighing scale at each visit. Tolerability of the diet and any adverse events will be evaluated by means of parental interview using the study proforma at each visit. Parents will be additionally questioned for the following symptoms - vomiting, lethargy, poor appetite, refusal to feed and constipation. Any other parental concerns will also be noted.

The details of laboratory tests (blood and urine) that will be performed at each hospital visit have been highlighted in figure 2. All of these are standard tests for dietary therapy except blood PUFA levels. No additional phlebotomy will be done for blood PUFA levels, and sample for the blood PUFA will be collected along with sampling for standard tests. Additionally these children will be subjected to EEG, ECG and ultrasound KUB at baseline and 24 weeks.

At 3 and 6 months these children will be also be subjected to cognition and behaviour assessment. The assessment of cognition will be performed using Vineland Social Maturity Scale and the results will be noted for each domain separately. The behavioural assessment will be done using Child Behavior Checklist (CBCL). The result will be filed for each domain separately. The details of investigations/ assessments have been highlighted in figure 2.

Parents will be instructed to contact either Pediatric Emergency department of our Institute or the principle investigator in case of any problems or acute adverse events are encountered.

Telephonic Followup

In addition, telephonic calls will be made twice a week to every patient to check and re-enforce dietary compliance, to record seizure frequency and to chronicle adverse events (if any).

Withdrawal from study

Patients may withdraw from the study or may be withdrawn at the request of the investigator. The reason of withdrawal will be recorded. Reasons for withdrawal from the study may include: withdrawal of permission to use patient specific data for analysis, significant subject noncompliance (defined as adherence to diet for <80% duration; i.e, 19weeks), dietary failure (no reduction in seizure frequency/ increase in seizure frequency, despite dietary therapy for 12 weeks), and fasting serum cholesterol more than 300mg/dL. Reasons for withdrawal from study protocol will be defined and recorded by the investigator in patients' record.

Figure 1. Flow of patients
KD= Ketogenic Diet; MAD= Modified Atkins Diet; LGIT= Low Glycemic Index Therapy Diet

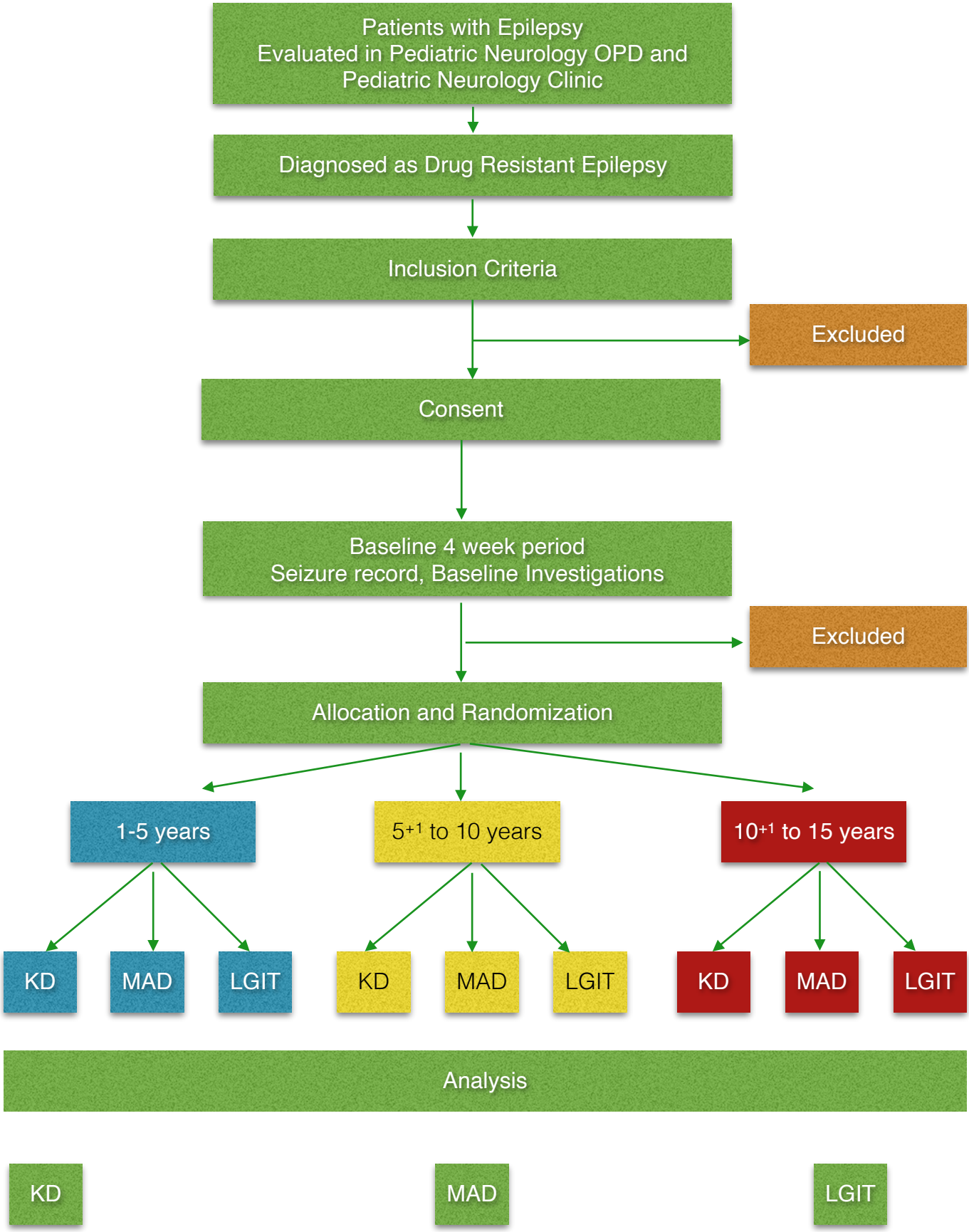

Figure 2. Details of investigations/assessments during study

	Run in of 4 weeks	**Treatment phase**			
Drug status	No Drugs; Baseline workup and allocation of intervention arm	Initiation of Diet based on allocation	Either Ketogenic diet, Modified Atkins Diet, Low Glycemic Index Therapy depending upon allocation		
Week	Week -4 to 0	0	4	12	24
Visit	1	2	3	4	5
Assessments Shift Syrups to Tablets Sugar Free toothpaste					
Clinical					
- Anthropometry	+	+	+	+	+
- Mean weekly Seizure frequency in last 4 weeks	+	+	+	+	+
- Adverse events assessment			+	+	+
- Compliance Check		+	+	+	+
EEG	+	-	+		+
ECG	+	If Clinically Indicated			+
Laboratory					
- CBC	+		+	+	+
- Blood sugar (Fasting)	+		+	+	+
- ABG including Lactate	+		+	+	+
- LFT incl ALT, AST, ALP	+		+	+	+
- RFT	+		+	+	+
- Spot Urinary Ca/ Cr ratio	+		+	+	+
- Fasting Lipid Profile	+		+	+	+
- Na, K, Ca, PO4,	+		+	+	+
- Serum Cu, Zn, Retinol, Vitamin E**	+		-	-	+
- Blood PUFA levels	+		-	-	+
USS KUB	+	If Clinically Indicated			+
IQ Assessment Behavioural Assessment	+			+	+

Safety Assessment

All the three dietary regimen have been used for drug resistant epilepsy for more than a decade. However, of safety assessment, Dr Ashok Deorari, Professor, Department of Pediatrics, will be the monitor of study. The assessment of safety profile will be performed after 80 patients have been enrolled for the study and earlier at the discretion of the monitor.

Statistical analysis

General

Analyses will be performed according to the CONSORT statement. Both intention to treat and perprotocol analyses will be performed. Continuous variables will be summarised with standard descriptive statistics including means, standard deviations, medians and ranges. Categorical variables will be summarised using means, frequencies and percentage. Ninety-five percent confidence intervals (CI) will be provided for descriptive statistics as warranted. The primary objective of study (percentage of seizure reduction) between the three arms (KD, LGIT, and MAD) at 24 weeks will be compared by estimating effect size and determining its 95% CI. Differences among comparison groups in continuos variables will be estimated using student t-test for normal distribution variables and using Mann-Whitney U test for variables that do not follow normal distribution. Differences in categorical variables will be assessed using Chi-square test or Fischer exact test. A p-value < 0.05 will be considered to indicate a statistically significant result.

Missing or incomplete values

Every effort will be made to collect all data at specified times. If data are incomplete and whenever it is not possible to reliably asses for primary outcome, these data will be defined as indeterminate.

Data management

Data will be recorded on the case record form (CRF) by the investigator. Results of laboratory examination, ultrasound and all followup visits will be recorded on the CRF. The original signed consent form for each participating patient will also be kept along with CRF. The data will be transferred from the CRF to electronic format by the primary investigator and checked by coinvestigator for its accuracy. The research records will be maintained by the investigator and will be considered as the source documents for the purpose of auditing the study.

Sample Menus

Ketogenic Diet

Meal 1: Scrambled eggs + 15 grams apple

Meal 2: Paneer subzi (Paneer + Cream + Tomato + Cooking Oil)

Meal 3: Cauliflower subzi (Cauliflower + Cheese + Cream + Cooking oil)

Meal 4: Chicken Soup (Chicken + carrots + oil + cream)

Modified Atkins Diet

Meal 1: Milk 30 ml + soya flour

Meal 2: Pumpkin kheer (50 grams of pumpkin in 15 ml cream + soya milk + Oil)

Meal 3: Tomato soup (50 grams of tomato + butter/ cream + salt)

Meal 4: Egg (omelette) with vegetables

Low Glycemic Index Therapy Diet

Meal 1: Porridge with milk, soya flour/ egg

Meal 2: Vegetables cooked with oil

Meal 3: Cream of chicken soup

Meal 4: Mixed vegetable soup

Individualized Diet Plan

1. The dietary intake over the past 3 days would be discussed with the parents to understand their staple diet and then the menu and dietary advice would be given based on the regularly used items in the their kitchen.
2. The menus will be individualized based on personal choices; for example vegetarian/ non-vegetarian, specific food choices or aversions that the child has.
3. Parents will be counseled regularly to avoid monotony of food and will be given choices and food replacements.
4. The menus and the techniques to prepare them would be done individually with each parent by the dietician.
5. No extra/ specific packaged food will be advised.

Unique ID: _____ Type of Diet: A/ B/ C

Date तारीख	Seizures दौरे	Ketones पिशाब	Vomiting उलटी	Diarrhoea Constipation कबज	Fever बुखार	Number of meals खाना	Others अनय

Date तारीख	Seizures दौरे	Ketones पिशाब	Vomiting उलटी	Diarrhoea Constipation कबज	Fever बुखार	Number of meals खाना	Others अनय

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Supplementary Appendix 2. Schedule of enrollment and evaluations.

	Run-in	Randomization	Treatment Phase*					
	- Baseline Seizure - Switch from syrups to tablets - Sugar free toothpaste	Diet Initiation	- Ketogenic Diet - Modified Atkins diet - Low Glycemic Index Therapy Diet					Primary Outcome ⬇
WEEK	-4	0	4	8	12	16	20	24
Visit**	✓	✓	✓		✓			✓
Clinical assessment	✓	✓	✓		✓			✓
Lab	✓		✓		✓			✓
EEG	✓		✓		✓			✓
USS	✓							✓

* All diets were supplemented with multivitamins and minerals as follows: vitamin C 100 mg, niacinamide 50 mg, vitamin B1 10 mg, vitamin B2 10 mg, vitamin B6 3 mg, calcium pantothenate 12.5 mg, folic acid 1 mg, vitamin B12 5 mcg, vitamin A acetate 500 IU, vitamin D3 500 IU, vitamin E acetate 25 IU, zinc oxide 15 mg, cupric oxide 2.5 mg, sodium selenate 60 mcg, manganese chloride 1.4 mg, chromic chloride 65 mcg

** All clinical visits were supplemented with twice a week telephone calls between the clinical visit to reinforce dietary compliance, monitor for adverse events and address any specific concerns.

EEG=Electroencephalogram; USS= Ultrasonography

Supplementary Appendix 3. Details of clinical evaluation and investigations performed at each hospital visit.

	Run in of 4 weeks	**Treatment phase**			
Drug status	**No Drugs; Baseline workup and allocation of intervention arm**	**Initiation of Diet based on allocation**	**Either Ketogenic diet, Modified Atkins Diet, Low Glycemic Index Therapy depending upon allocation**		
Week	Week -4 to 0	0	4	12	24
Visit	1	2	3	4	5
Assessments	Shift Syrups to Tablets Sugar Free toothpaste				
Clinical					
- Anthropometry	+	+	+	+	+
- Mean weekly Seizure frequency in last 4 weeks	+	+	+	+	+
- Adverse events assessment		+	+	+	+
- Compliance Check			+	+	+
EEG	+	-	+		+
ECG	+	If Clinically Indicated			+
Laboratory*					
- CBC	+		+	+	+
- Blood sugar (Fasting)	+		+	+	+
- ABG including Lactate	+		+	+	+
- LFT incl ALT, AST, ALP	+		+	+	+
- RFT	+		+	+	+
- Spot Urinary Ca/ Cr ratio	+		+	+	+
- Fasting Lipid Profile	+		+	+	+
- Na, K, Ca, PO4	+		+	+	+
- Serum Cu, Zn, Se	+		-	-	+
Ultrasound KUB	+	If Clinically Indicated			+
IQ Assessment Behavioural Assessment	+			+	+

*Serum 25-hydroxyvitamin D levels and carnitine profiles were not checked

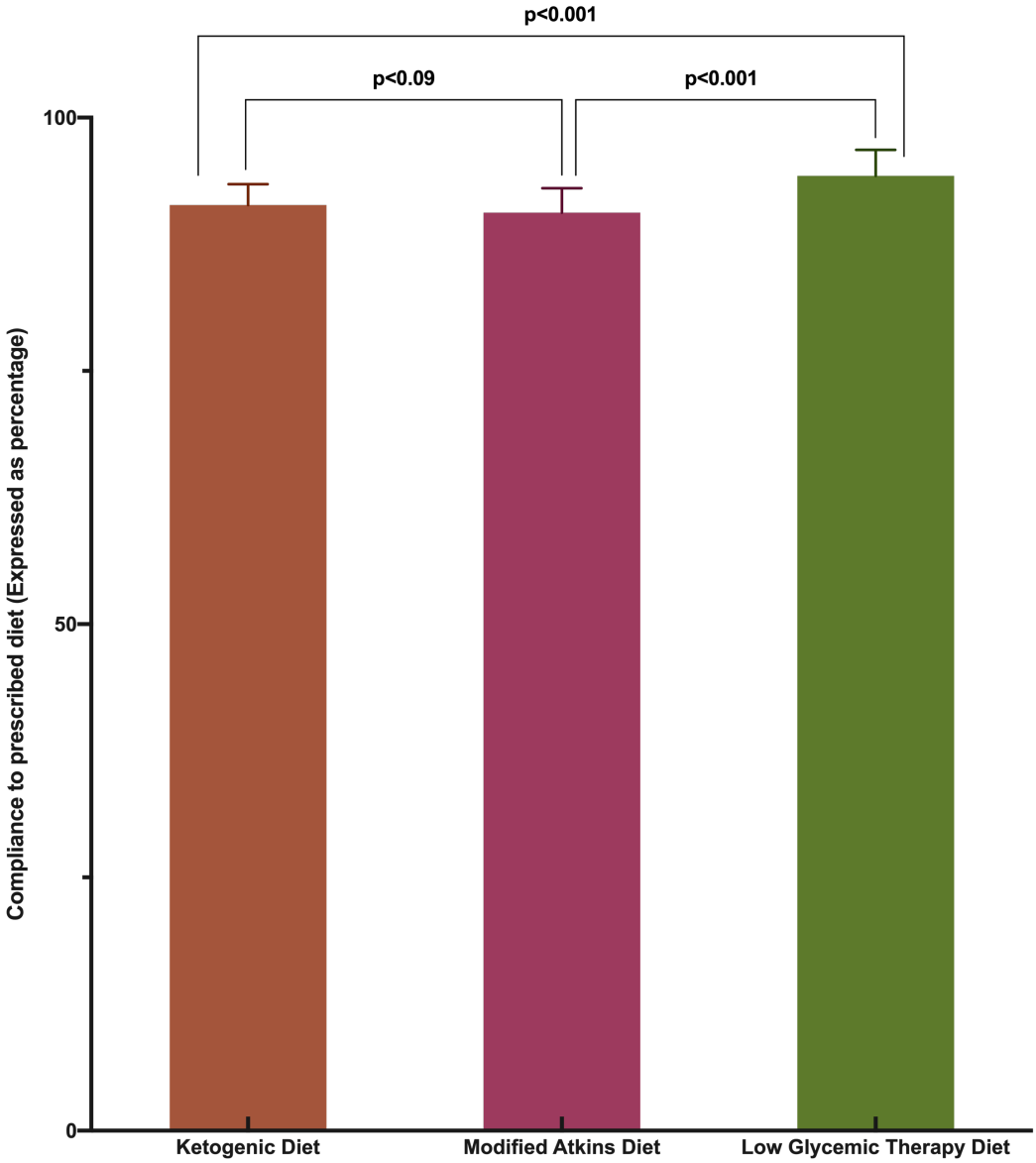
Supplementary Appendix 4. Etiology of drug-resistant epilepsy in enrolled patients.

Etiology	**KD N=55**	**MAD N=58**	**LGIT N=57**
Structural epilepsy secondary to acquired causes, n (%)	33 (60%)	41 (70.7%)	41 (71.9%)
Perinatal asphyxia	26	25	27
Hypoglycemia	6	5	6
Neonatal sepsis	6	2	3
Stroke (post-neonatal)	1	1	0
Post-neonatal meningo-encephalitis	3	7	6
Genetic Epilepsy, n (%)	16 (29.1%)	12 (20.7%)	14 (24.6%)
SCN1a	5	3	5
SCN9a	2	2	3
SCN2a	1	1	0
PRRT2	2	1	0
DEPDC5	2	1	1
CLCN5	0	1	2
KCNQ2	2	1	1
PCDH19	2	2	1
STXBP1	0	0	1
Genetic epilepsy with structural abnormality, n	6 (10.9%)	5 (8.6%)	2 (3.5%)
Tuberous sclerosis	4	3	1
Lissencephaly	2	2	1
(KD = Ketogenic diet; MAD = Modified Atkins Diet; LGIT = Low Glycemic Index Therapy Diet)			

Supplementary Appendix 5. Details of antiseizure drugs received by the patients.

	KD N=55	MAD N=58	LGIT N=57
Valproate, n (%)	55 (100%)	55 (94.8%)	55 (96.5%)
Clonazepam, n (%)	35 (63.6%)	40 (69%)	33 (57.9%)
Clobazam, n (%)	20 (36.4%)	18 (31%)	22 (38.6%)
Levetiracetam, n (%)	43 (78.2%)	46 (79.3%)	42 (73.7%)
Topiramate, n (%)	6 (10.9%)	12 (20.7%)	14 (24.6%)
Lamotrigine, n (%)	8 (14.5%)	12 (20.7%)	11 (19.3%)
Zonisamide, n (%)	17 (30.9%)	17 (29.3%)	19 (33.3%)
Phenytoin, n (%)	2 (3.6%)	3 (5.2%)	4 (7%)
Phenobarbitone, n (%)	4 (7.3%)	4 (6.9%)	2 (3.5%)
Lacosamide, n (%)	0	2 (3.4%)	4 (7%)
Oxcarbazepine, n (%)	4 (7.3%)	0	0
ACTH*, n (%)	35 (63.6%)	40 (69%)	40 (70.2%)
Vigabatrin*, n (%)	35 (63.6%)	40 (69%)	40 (70.2%)
*ACTH and vigabatrin were administered in past. None of the patients at time of initiating intervention was on ACTH or vigabatrin			
Abbreviations: KD= Ketogenic Diet; MAD= Modified Atkins Diet; LGIT= Low Glycemic Index Therapy diet; ACTH= Adrenocorticotrophin			

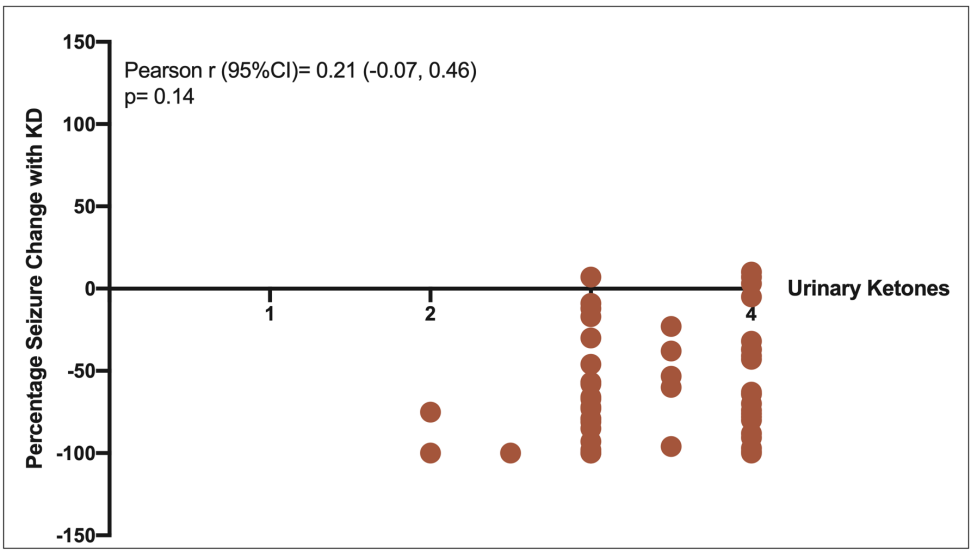
Supplementary Appendix 6. The compliance to diet was calculated as percentage based on record maintained by parents. The denominator was number of diets prescribed for a given duration (for example, 4 diets per day were prescribed for ketogenic diet (KD); hence number of KD diets over 4 weeks for a child would be 4*28=112, the denominator). The numerator was the number of prescribed diets actually taken by the child. The compliance was significantly better with LGIT as compared to KD and MAD. The compliance was comparable between KD and MAD.



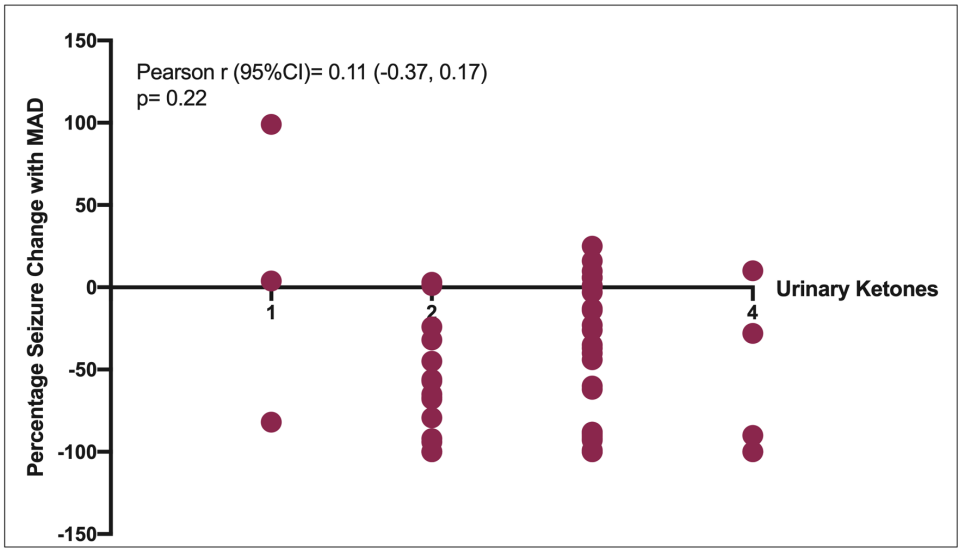
	Ketogenic Diet	Modified Atkins Diet	Low Glycemic Therapy Diet
Mean (±sd)	91.4 (±2%)	90.6 (±2.4%)	94.3 (±2.6%)
Median (Range)	91.5 (84.8-94.9%)	90.8 (84.4-95%)	94.8 (82.5-97.2%)

Supplementary Appendix 7. The percentage change in seizure frequency (Y-axis) was correlated with urinary ketones (X-axis) for Ketogenic Diet (KD, Figure SA 7a), Modified Atkins diet (MAD, SA 7b) and Low Glycemic Index Therapy (LGIT, SA 7c). The change in seizure frequency did not correlate with urinary ketones for any of the interventions.

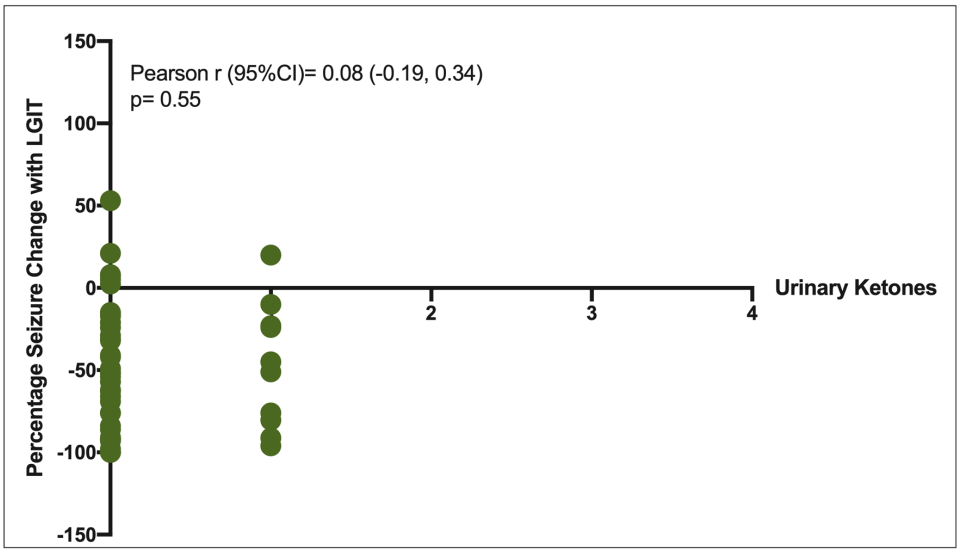
SA 7a



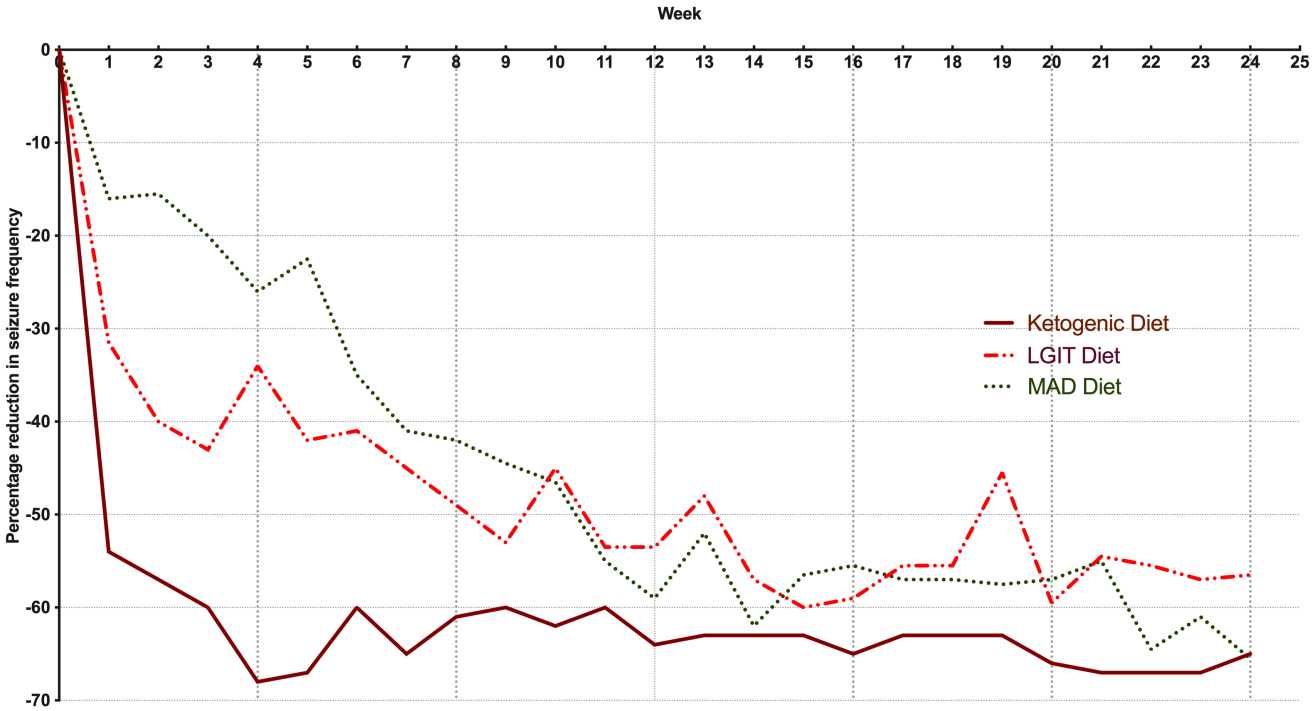
SA 7b



SA 7c



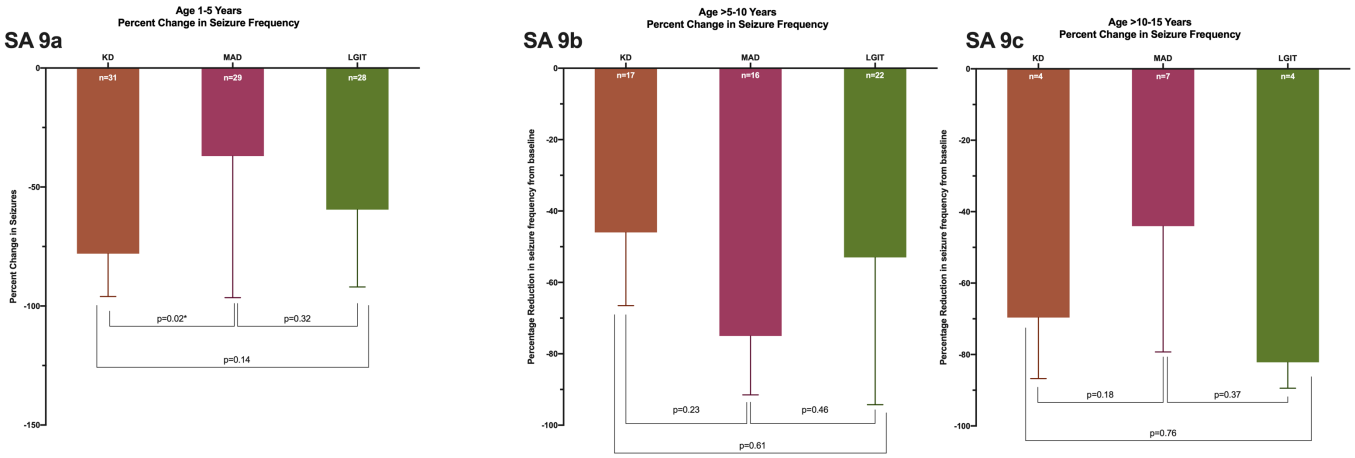
Supplementary Appendix 8. The median percentage change in seizure frequency (Y-axis) is represented as a function of time for each of interventions: Ketogenic Diet (KD), Modified Atkins diet (MAD) and Low Glycemic Index Therapy (LGIT). The table beneath the graph depicts the number of patients (n) on diet at that time point and the mean (SD) percentage reduction and median (IQR) percentage reduction in seizure frequency.



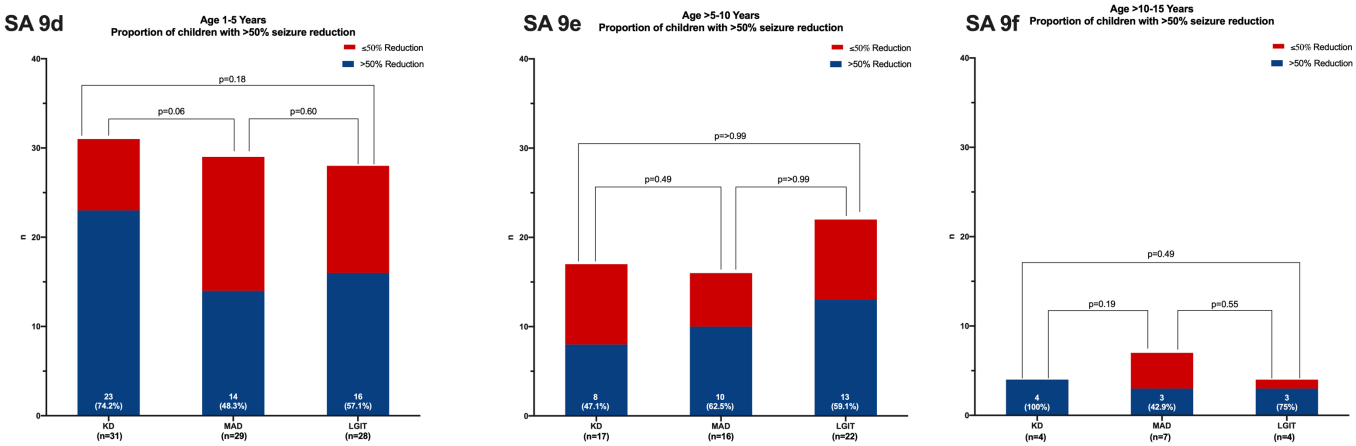
KD n	53	53	53	53	52	52
Mean (SD)	51% (56.7)	50.4% (60.1)	52.8% (50.1)	55.4% (42.6)	59.4% (33.1)	60.8% (33.8)
Median (IQR)	-68% (-85 to -26)	-61% (-87 to -34)	-64% (-91 to -27)	-65% (-82 to -34)	-66% (-89 to -36)	-65% (-91 to -40)
MAD n	55	55	54	52	52	52
Mean (SD)	40.1% (48.2)	47.4% (41)	45.4% (46.3)	50.5% (41.8)	47.9% (49.8)	49.3% (44.7)
Median (IQR)	-34% (-83 to -10)	-49% (-87 to -23)	-54% (-82 to -12)	-59% (-92 to -17)	-60% (-91 to -13)	-57% (-95 to -18)
LGIT n	55	54	54	54	54	54
Mean (SD)	33.1% (46.6)	40.3% (49.7)	52.9% (38.6)	55.4% (38.8)	55% (38)	57.1% (38.8)
Median (IQR)	-26% (-74 to -4)	-42% (-85 to -11)	-59% (-92 to -17)	-55.5% (-94 to -27)	-57% (-92 to -25)	-65.5% (-92 to -25)

Supplementary Appendix 9. Subgroup analysis were performed for percentage change in seizure frequency and proportion of children with >50% seizure reduction. The subgroups were defined based on age: 1 to 5 years, >5 to 10 years and >10 to 15 years. SA 9a, 9b and 9c depict the percentage change in seizure frequency (median and IQR) for each subgroup. The median (IQR) percent change in seizure frequency in age group 1 to 5 years was (SA 8a): KD = -78 (-96 to -43); MAD = -37 (-96 to -43); and LGIT = -60 (-92 to -30). In the age group >5 to 10 years, the median (IQR) percent change in seizure frequency was (SA 8b): KD = -46 (-67 to -3); MAD = -75 (-92 to -31); and LGIT = -53 (-94 to -14). The median (IQR) percent change in seizure frequency in age group >10 to 15 years was (SA 8c): KD = -70 (-87 to -56); MAD = -44 (-79 to -6); and LGIT = -82 (-89 to -18). SA 9d, 9e, 9f depict the proportion of children with >50% seizure reduction based on age. The statistically significant results have been depicted with an asterisk (*).

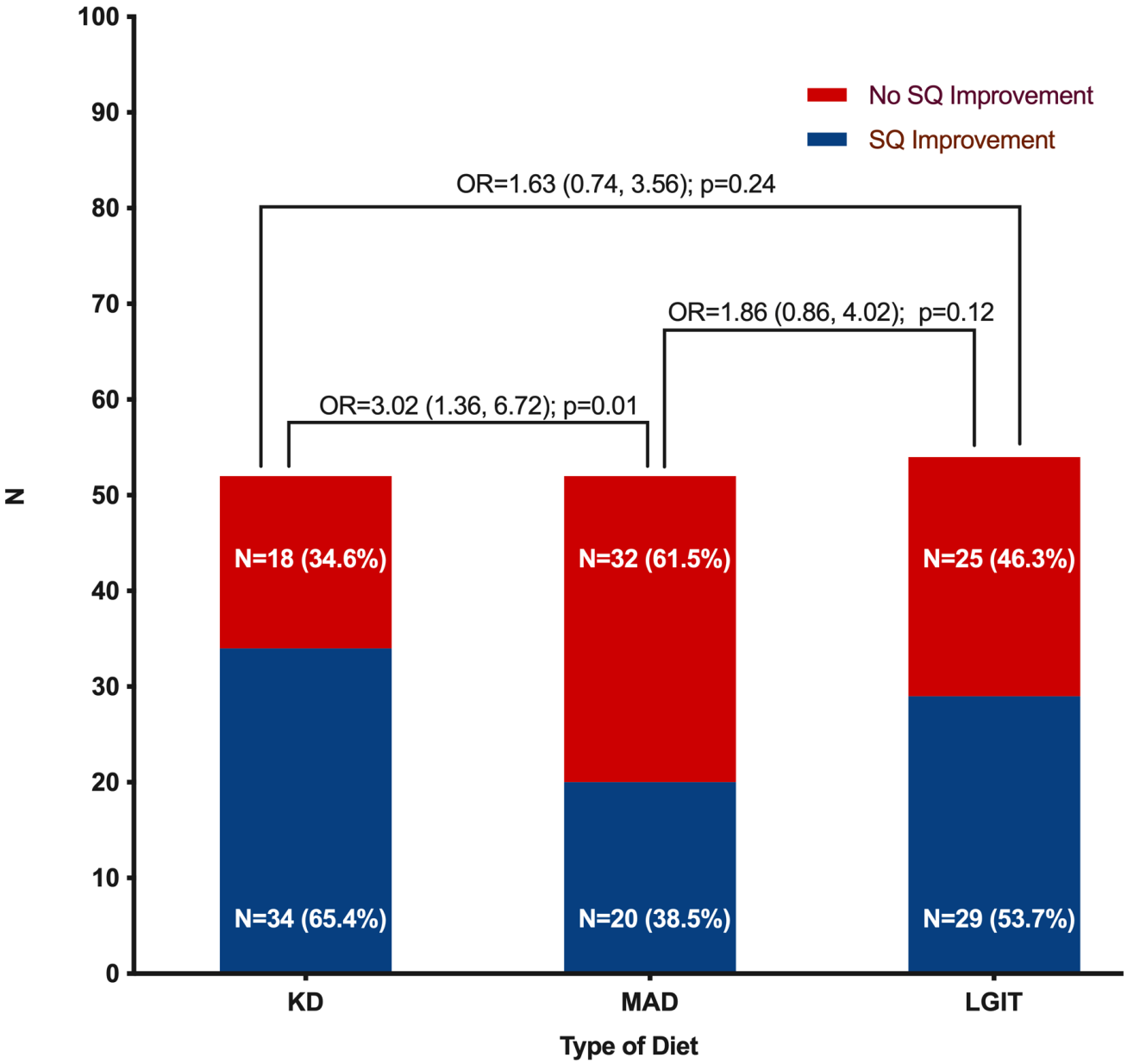
Subgroup analysis of percent change in seizure frequency based on age



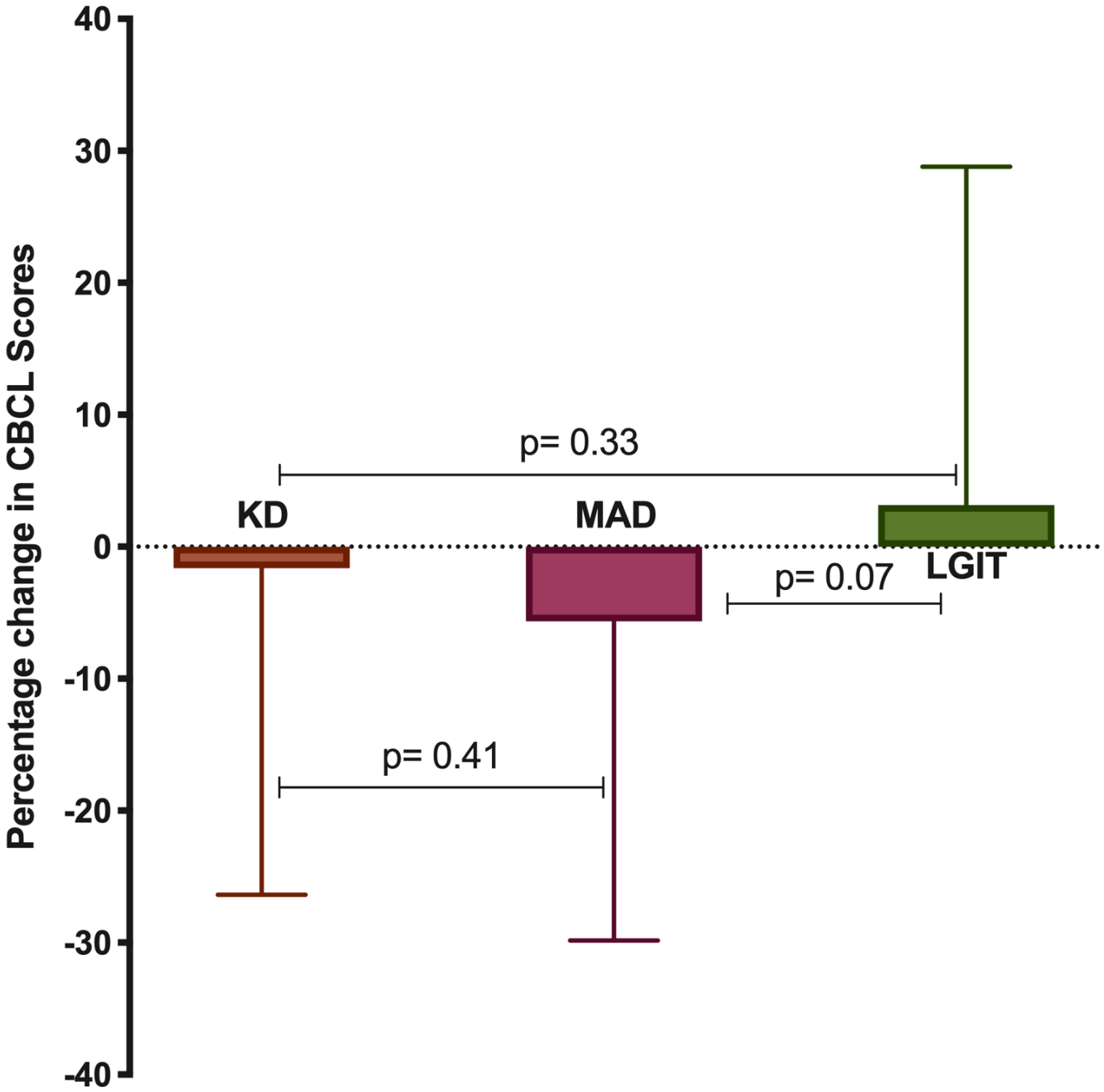
Subgroup analysis of proportion of children with >50% seizure reduction based on age



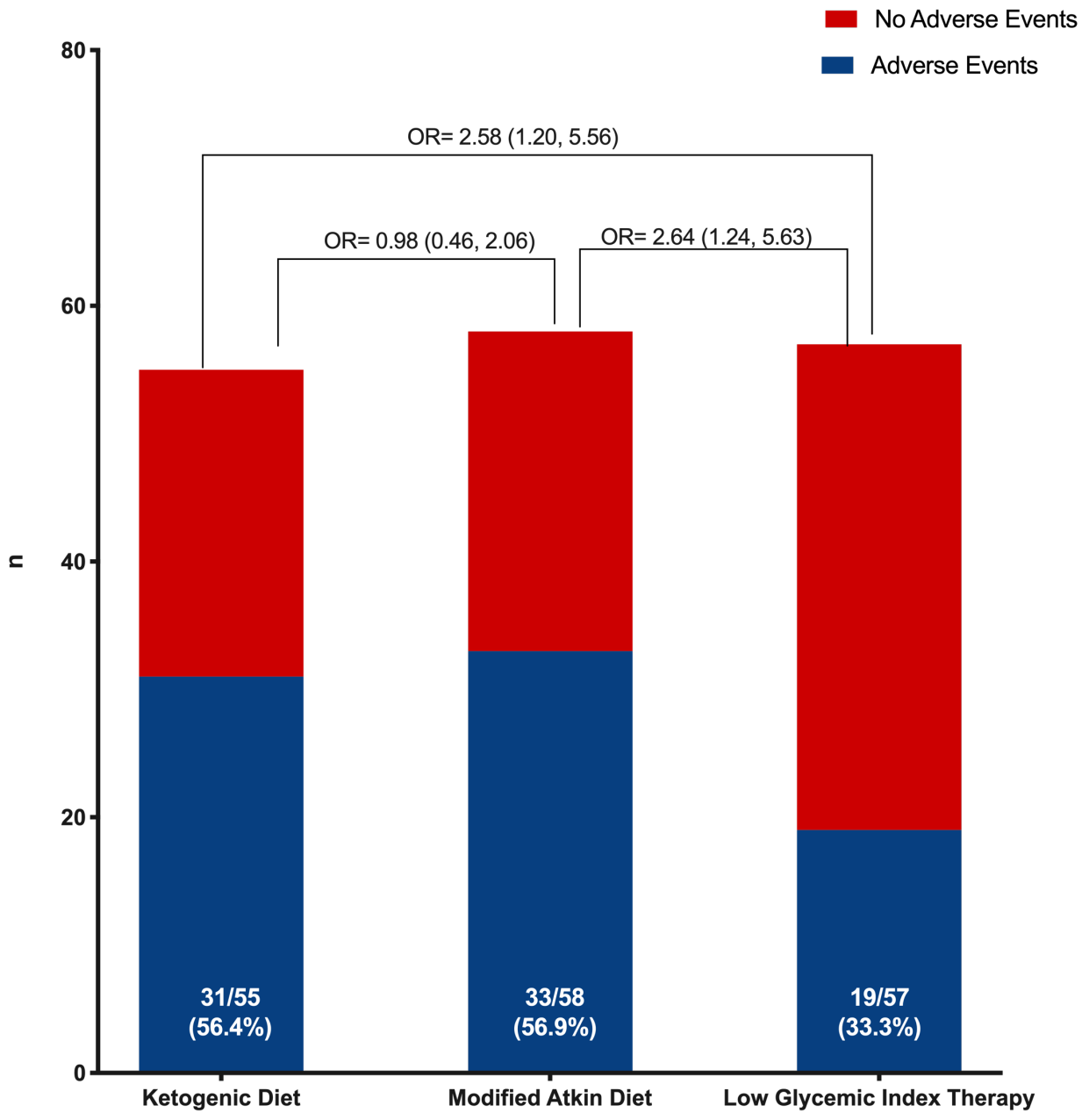
Supplementary Appendix 10. **SA 10a**. The bars indicate the proportion of children showing improvement in their Social Quotient (SQ) after intervention. The SQ was assessed using Vineland Scale for Social Maturity. The change in SQ was significantly better with Ketogenic Diet (KD) than Modified Atkins Diet (MAD) (Odds ratio [OR] = 3.02; 95%CI = 1.36, 6.72, p = 0.01), while the improvement was comparable between KD and Low Glycemic Index Therapy (LGIT) interventions (OR = 1.63; 95%CI = 0.74, 3.56, p = 0.24) and between MAD and LGIT groups (OR = 1.86; 95%CI = 0.86, 4.02, p = 0.12).



SA 10b. The behavioral change was assessed with Childhood behavioral checklist. The percentage change in behavioral score after interventions were compared between Ketogenic Diet (KD), Modified Atkins Diet (MAD) and Low Glycemic Index Therapy). The change in scores was insignificant for all three arms



Supplementary Appendix 11. Bar graphs depicting proportions of patients with treatment emergent adverse events with each intervention. Odds ratio (OR) with 95% confidence interval are shown.

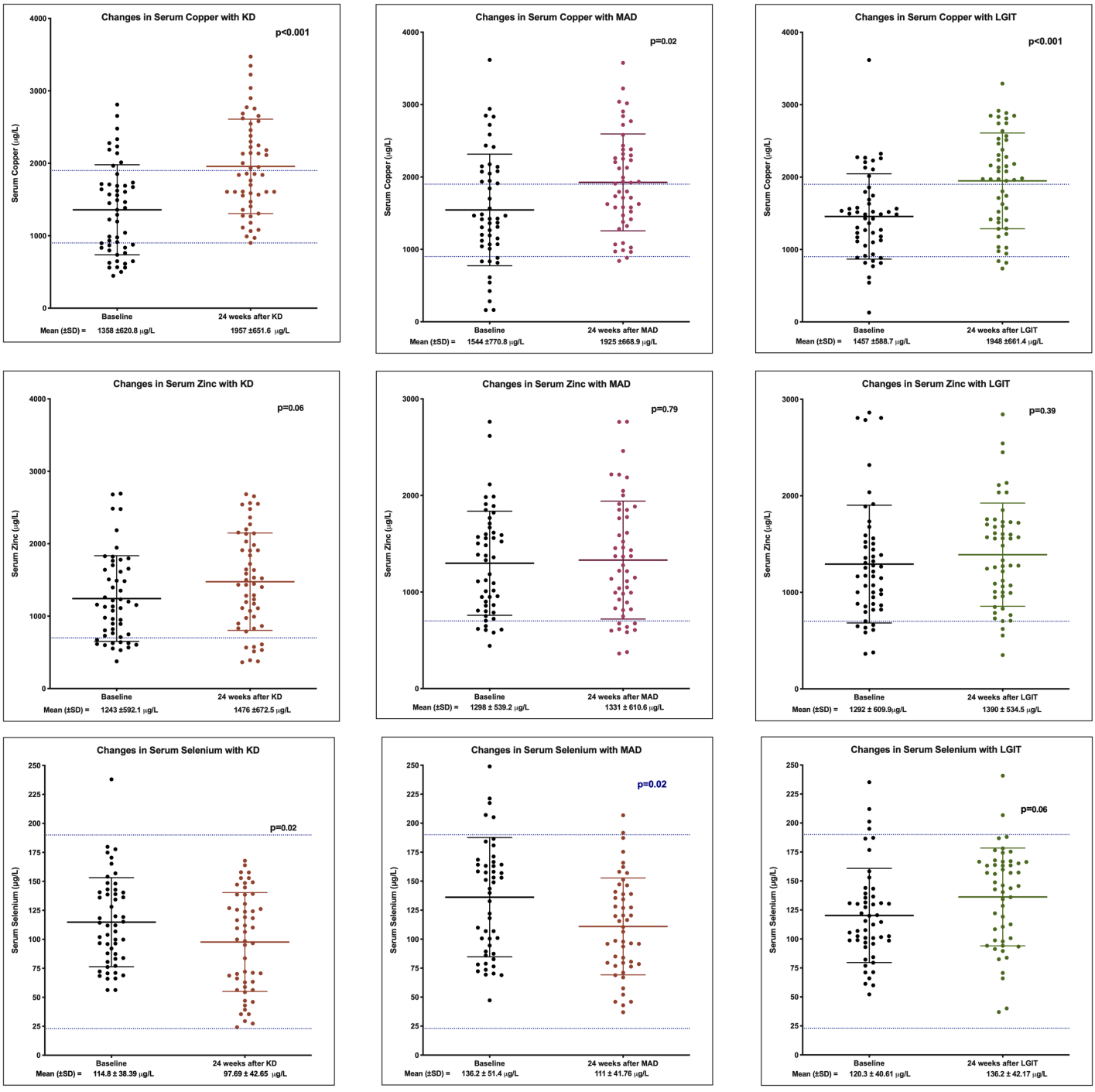


Supplementary Appendix 12. The incidence of adverse events across the various intervention arms.

Adverse event	KD, N (%) n = 55	MAD N (%) n = 58	LGIT N (%) n = 57	p
Clinical				
Vomiting	28 (50.9%)	26 (44.8%)	18 (31.6%)	0.12
Diarrhea	8 (14.5%)	8 (13.8%)	8 (14%)	0.79
Constipation	25 (45.5%)	19 (32.8%)	18 (31.6%)	0.58
Febrile illness requiring hospitalization	9 (16.4%)	5 (8.6%)	1 (1.8%)	0.39
Sleep Disturbance	2 (3.6%)	2 (3.4%)	3 (5.3%)	0.34
Decreased satiety	23 (41.8%)	4 (6.9%)	0	<0.0001
Investigations				
Thrombocytopenia	1 (1.8%)	0	2 (3.5%)	0.14
Transaminitis up to 2 times upper limit normal	16 (29.1%)	12 (20.7%)	8 (14%)	0.15
Transaminitis >5 times upper limit normal	2 (3.6%)	1 (1.7%)	0	0.35
Asymptomatic hypoglycemia	1 (1.8%)	0	0	NA
Hyperuricemia	2 (3.6%)	4 (6.9%)	0	0.13
Metabolic acidosis below 7.3	3 (5.5%)	1 (1.7%)	0	0.35
Hypocalcemia	1 (1.8%)	0	0	NA
Hypercalciuria	4 (7.3%)	6 (10.3%)	0	0.07
Nephrocalcinosis	0	2 (3.4%)	0	0.13
Fracture after trivial trauma	0	1 (1.7%)	0	NA
Dyslipidemia	16 (29.1%)	14 (24.1%)	9 (15.8%)	0.22
Hypercholesterolemia	9 (16.4%)	9 (15.5%)	7 (12.3%)	0.78
Hypertriglyceridemia	7 (12.7%)	6 (10.3%)	4 (7%)	0.59
High LDL	8 (14.5%)	8 (13.8%)	7 (12.3%)	0.92
Low HDL	3 (5.5%)	1 (1.7%)	0	0.16
Prolonged QTc	2 (3.6%)	1 (1.7%)	0	0.35
Scurvy	0	2 (3.4%)	0	NA

(KD = Ketogenic Diet; MAD = Modified Atkins diet; LGIT = Low Glycemic Index Therapy diet)

Supplementary Appendix 13. The plots depict the change in serum levels of zinc, copper and selenium with administration of Ketogenic Diet (KD), Modified Atkins Diet (MAD) and Low Glycemic Index Therapy (LGIT). The perforated lines in each graph depict the normal serum levels of micronutrients. The samples were analyzable for 52 patients of KD, 49 patients of MAD and 51 patients who were administered LGIT. After the intervention, all children showed a significant improvement in serum copper levels. There was a significant decline in serum levels of selenium with administration of KD and MAD. All children were on vitamin and micronutrient supplementation as shown in Figure 1



Supplementary Appendix 14. Anthropometric details of children receiving ketogenic diet (KD), Modified Atkin Diet (MAD) and Low Glycemic Index Therapy (LGIT).

Variable	KD	MAD	LGIT	p
Baseline				
Weight Mean (SD) Median (IQR)	17.48 (9.03) 14.25 (10.33-23.25)	17.12 (9.79) 13.75 (10.98-19.53)	16.76 (8.16) 14.50 (11.45-20.35)	0.92
Height Mean (SD) Median (IQR)	1.05 (0.19) 1.03 (0.90-1.18)	1.03 (0.20) 1.01 (0.89-1.14)	1.06 (0.18) 1.03 (0.93-1.16)	0.81
BMI Mean (SD) Median (IQR)	14.81 (2.96) 14.19 (12.58-16.73)	15.10 (3.27) 14.83 (12.89-16.07)	14.36 (2.47) 14.34 (12.70-15.80)	0.94
Week 4				
Weight Mean (SD) Median (IQR)	n=53 17.49 (8.84) 14.60 (10.60-22.85)	n=56 17.59 (9.86) 14.10 (11.20-20.08)	n=54 17.17 (8.20) 15 (11.95-20.35)	0.97
Height Mean (SD) Median (IQR)	1.05 (0.18) 1.01 (0.90-1.17)	1.04 (0.20) 1.01 (0.88-1.14)	1.07 (0.18) 1.03 (0.94-1.16)	0.73
BMI Mean (SD) Median (IQR)	14.99 (2.89) 14.25 (12.76-16. 76)	15.49 (3.24) 15.16 (13.66-16.94)	14.50 (2.37) 14.57 (12.88-15.88)	0.19
Week 12				
Weight Mean (SD) Median (IQR)	n=53 17.76 (8.82) 15.00 (11.00-22.90)	n=54 17.33 (9.23) 14.70 (11.60-20.30)	n=54 17.63 (8.26) 15.15 (12.33-21.03)	0.97
Height Mean (SD) Median (IQR)	1.05 (0.18) 1.02 (0.91-1.17)	1.04 (0.20) 1.01 (0.88-1.14)	1.07 (0.18) 1.03 (0.94-1.16)	0.68
BMI Mean (SD) Median (IQR)	15.18 (2.79) 14.43 (13.08-16.98)	15.53 (3.33) 15.44 (13.73-17.19)	14.84 (2.46) 14.75 (13.42-16.28)	0.46
Week 24				
Weight Mean (SD) Median (IQR)	18.39 (8.79) 15.90 (12.03-20.80)	18.48 (9.96) 15 (12.03-20.80)	18.15 (8.42) 15.40 (12.50-21.85)	0.98
Height Mean (SD) Median (IQR)	1.06 (0.18) 1.04 (0.92-1.17)	1.04 (0.20) 1.02 (0.89-1.15)	1.08 (0.18) 1.05 (0.94-1.20)	0.68
BMI Mean (SD) Median (IQR)	15.53 (2.76) 14.94 (13.28-17. 13)	16.14 (31.5) 15.75 (14.28-17.38)	15.08 (2.50) 14.76 (13.28-16.96)	0.15