Published Ahead of Print on January 4, 2023 as 10.1212/WNL.0000000000206776

Neurology®

The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print

DOI: 10.1212/WNL.0000000000206776

Safety, Efficacy, and Tolerability of Modified Atkins Diet in Persons With Drug-Resistant Epilepsy: A Randomized Controlled Trial

Author(s):

Mala Manral, PhD[1]; Rekha Dwivedi, PhD[1]; Sheffali Gulati, MD,DM[2]; Kirandeep Kaur, PhD[1]; Ashima Nehra, PhD[3]; Ravindra Mohan Pandey, PhD[4]; Ashish Datt Upadhyay, PhD[4]; Savita Sapra, PhD[2]; Manjari Tripathi, MD,DM[1]

Corresponding Author:

Manjari Tripathi, mtripathiaiims@gmail.com

Affiliation Information for All Authors: 1.Department of Neurology, All India Institute of Medical Science, New Delhi-29; 2.Department of Paediatrics, All India Institute of Medical Science, New Delhi-29; 3.Department of Neuropsychology, All India Institute of Medical Science, New Delhi-29; 4. Department of Biostatistics, All India Institute of Medical Science, New Delhi-29

Equal Author Contribution:

Contributions:

Mala Manral: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Rekha Dwivedi: Drafting/revision of the manuscript for content, including medical writing for content

Sheffali Gulati: Drafting/revision of the manuscript for content, including medical writing for content; Additional contributions: Helped in writing of manuscript - Revision of Manuscript writing - Ravindra Mohan Pandey Revision of Manuscript writing - Ashish Datt Upadhyay Revision of manuscript - Savita Sapra Support for Research grant. - Manjari Tripathi

Kirandeep Kaur: Drafting/revision of the manuscript for content, including medical writing for content

Ashima Nehra: Drafting/revision of the manuscript for content, including medical writing for content

Ravindra Mohan Pandey: Analysis or interpretation of data; Additional contributions: Helped in writing of manuscript - Sheffali Gulati Revision of Manuscript writing - Revision of Manuscript writing - Ashish Datt Upadhyay Revision of manuscript - Savita Sapra Support for Research grant. - Manjari Tripathi

Ashish Datt Upadhyay: Analysis or interpretation of data; Additional contributions: Helped in writing of manuscript - Sheffali Gulati Revision of Manuscript writing - Ravindra Mohan Pandey Revision of Manuscript writing - Revision of manuscript - Savita Sapra Support for Research grant. - Manjari Tripathi

Savita Sapra: Drafting/revision of the manuscript for content, including medical writing for content; Additional contributions: Helped in writing of manuscript - Sheffali Gulati Revision of Manuscript writing - Ravindra Mohan Pandey Revision of Manuscript writing - Ashish Datt Upadhyay Revision of manuscript - Support for Research grant. - Manjari Tripathi
Manjari Tripathi: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Additional contributions: Helped in writing of manuscript - Sheffali Gulati Revision of Manuscript writing - Ravindra Mohan Pandey Revision of Manuscript writing - Ashish Datt Upadhyay Revision of manuscript - Savita Sapra Support for Research grant.

Figure Count:

2

Table Count:

3

Search Terms:

[20] Clinical trials Randomized controlled (CONSORT agreement), [60] All Epilepsy/Seizures, [112] Outcome research, [205] Neuropsychological assessment, Modified Atkins Diet, [323] Class III

Acknowledgment:

This study was part of Doctoral of Philosophy (PhD) research work. We acknowledge the support of, Department of Biostatistics, AIIMS, for analysing the data and members who helped in our study: Mr Sanjay Kumar and Mrs Anuradha. Special thanks to the data safety monitoring board (DSMB) members: *Dr. Mani Kaliavani, PhD (Biostatistics, AIIMS, India), Dr.Sudhir Sarangi, MD, DM (Department of Pharmacology, AIIMS, New Delhi, India), Dr.Achal Shrivastava, MD, DM (Dept. of Neurology, AIIMS, New Delhi, India) and Dr. Rajesh Sagar (Dept. of Psychiatrist, AIIMS, New Delhi, India) . We also express our gratitude to the patients and their families for participating in this study.

Study Funding:

This trial was supported by the Centre of Excellence for epilepsy (COE)-Phase-II, which is funded by the Department of Biotechnology, Govt. of India. (Ref. No.: BT/MED/122/SP24580/2018) for AIIMS, New Delhi and NBRC, Manesar, Gurgaon (Haryana).

Disclosures:

The authors report no relevant disclosures.

Preprint DOI:

Received Date:

2022-05-18

Accepted Date:

2022-11-17

Handling Editor Statement:

Submitted and externally peer reviewed. The handling editor was Barbara Jobst, MD, PhD, FAAN.

Abstract

Background and objectives: Modified Atkins Diet (MAD) has emerged as an adjuvant therapy in drug-resistant epilepsy (DRE). Most studies are in children, there is limited evidence for DRE in in adults. The present study aimed to investigate if MAD along with standard drug therapy (SDT) was indeed more effective than SDT alone in reducing seizure frequency and improving psychological outcomes at 6 months in Adolescents and adults with DRE (non-surgical).

Methods: A prospective randomized controlled trial was conducted at tertiary care referral centre, in India. Persons with DRE aged 10-55 years attending outpatient epilepsy clinics between August 2015 and April 2019, who had more than two seizures/month despite using at least three appropriate anti-seizure medications (ASMs) at their maximum tolerated doses and had not been on any form of diet therapy for the past one year, were enrolled. Patients were assessed for the eligibility and randomly assigned to receive SDT plus MAD (intervention arm) or SDT alone (control arm).The primary outcome was>50% reduction in seizure- frequency, and the secondary

outcomes were quality of life (QOL), behaviour, adverse events and rate of withdrawal at six months. Intention to treat analysis was performed.

Results: 243 patients were screened for eligibility; 160 patients (80 adults and 80 adolescents) were randomized to either intervention or Control arm. Demographic and clinical characteristics in both groups were comparable at baseline. At six months > 50% seizure reduction was seen in 26.2% in the intervention group versus 2.5 % in the control group (95% CI 13.5-33.9; p<0.001). Improvement in QOL was 52.1±17.6 in the intervention group versus 42.5±16.4 in the control group (mean difference, 9.6; 95%CI 4.3 to 14.9, p<0.001). However, behaviour scores could be performed in 49 patients and improvement was seen in intervention versus control group (65.6±7.9 versus 71.4±8.1, p=0.015) at the end of the study. One patient had weight loss; two patients had Diarrhoea.

Discussion: MAD group demonstrated improvement in all aspects (reduction in seizure-frequency, and behavioural problems) compared to control group at the end of the study. MAD is an effective modality in controlling seizures, further research is required to assess its efficacy in terms of biomarkers along with descriptive metabolomics studies.

Trial Registration information: The clinical trial registry of India: CTRI/2015/07/006048.

Classification of Evidence: This study provides Class III evidence that the MAD increases the probability of seizure reduction in adolescents and adults with DRE.

INTRODUCTION:

Epilepsy affects more than 70 million people worldwide and one third of persons with epilepsy (PWE) are resistant to anti-seizure medications (ASMs) (1).

Drug-Resistant Epilepsy (DRE) is defined by the International League Against Epilepsy (ILAE) as ‘‘failure of adequate trials of two tolerated, appropriately chosen and used ASM schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom.”(2). Many patients who are not suitable surgical candidates or decline surgery (3) have benefited from dietary interventions (4),(5).

Modified Atkins Diet (MAD) aims to provide increase palatability and flexibility with a 1:1 ratio of fat to carbohydrates and protein as it has around 65% fat,25% protein and 10% carbohydrates (6) MAD and Low Glycemic Index Diet (LGIT) are hence less restrictive alternatives to the ketogenic-diet (KD) as protein and calories are not restricted (7).

In previous studies, nearly half the patients with DRE showed >50% seizure-reduction on the KD, and about 15-20% became seizure-free (8). A meta-analysis showed that the combined efficacy rates for freedom from seizures, reduction of seizures by 50% or more, and reduction of seizures

below 50% in adults with difficulty to treat epilepsy was 13%, 53%, and 27%, respectively (9). Several studies have shown an efficacy of MAD of at least in 30% of the study subjects having >50 % reduction in seizure (10),(11),(12),(13),(14).The efficacy of MAD has been established and well tolerated in children with DRE (13)(15),(16).Evidence suggests that MAD may have comparable efficacy but higher rate of compliance as compared to KD in adults with DRE (17),(18) ,(19),(20). There is an uncertainty as to the best dietary treatment due to low number of trials in adults with DRE (21),(22).Therefore, we chose MAD due to its ease of applicability and better compliance than the KD and the need for RCTs for assessing long-term outcomes with regards to the response to MAD in a larger cohort, including adolescents and adults with DRE which are still lacking.

We therefore performed a randomized controlled trial (RCT). Our primary research question was to investigate "if the addition of MAD (Dietary intervention) with on-going Standard Drug Therapy (SDT) is more efficacious in terms of seizure control at six months in the non-surgical patients with DRE?" The secondary objectives were to determine the quality of life, behaviour, tolerability of MAD and their adverse-effects at six months among adolescent and adults with DRE.

METHODS

Trial Design and Oversight

A prospective randomized open-label, blinded end-point (PROBE) controlled trial with two parallel arms design was conducted in the paediatric and adult neurology clinic, All India Institute of Medical Sciences (AIIMS), tertiary care referral centre in New Delhi, India. Eligible participants were randomly assigned to receive the SDT plus MAD or SDT alone in a 1:1 ratio. All the patients underwent clinical evaluations at baseline, 3 months and 6 months and outcome assessment was performed at 6 months. Structured formats of seizure-log, ketone-log, food-log, adverse-event diary and schedule of enrolment and timeline of clinical evaluations (eFigure 1A, 1B) are provided in eAppendix 1 in the Supplement.

Standard Protocol Approvals, Registrations, and Patient Consents

The Institutional Ethics Committee approved this trial and written informed consent was obtained from adults, parents or the legally authorized representatives of the adolescent patients with DRE, prior to recruitment. This trial was registered with the clinical trial registry of India [(CTRI); ref no. **CTRI/2015/07/006048**]. The report of the study follows the CONSORT guidelines.(23).

Participants

The detailed study flowchart is presented in (Figure 1).Potential candidates were recruited from the paediatric and neurology epilepsy clinic of Tertiary care referral centre, New Delhi. We enrolled patients who met the following inclusion criteria: 1) Age [10-55 years; adolescents (10 to ≤18 years) and adults (>18 to 55 years)]. 2) DRE who had more than two seizures per month despite using at least three appropriate ASMs at their maximum tolerated doses (21). 3) Agreed to regular follow-up and maintain their seizure-log. Patients were excluded in the following conditions: 1) surgical candidates2)an inborn error of metabolism, clinical suspicion of metabolic disorder (4)known chronic systemic disorder,3)intake of any dietary therapy in the past and 4) refusal to give consent. The screening procedure was carried out with the assistance of the concerned clinicians (MT and SG). All patients underwent - 4 weeks observation period (week -4 to week 0 (run-in period). Parents/caregivers were asked to maintain a daily seizure-log by recording the seizure type, duration, and frequency prior to enrolment. In the run-in period, no special dietary restrictions were advised. All baseline demographic, biochemical investigations and clinical details were collected in the paper-based standard case-report form and then entered in an excel datasheet after the run-in period.

Randomization and blinding

Patients were randomly assigned to either of the two groups- SDT plus MAD (intervention arm) or SDT alone (control arm). Computer-generated permuted blocks stratified by age group were used to generate a randomization list. Allocation concealment was performed using sealed and serially-numbered opaque envelopes. These envelopes were prepared by a person not involved in the study (RD). A dietician (MM) was directly involved with the diet prescription, and patients and their caregivers were not blinded to the treatment, seizures frequency and adverse events related to the treatment. Primary outcome-assessor (KK) was blinded to the treatment allocation. Secondary outcome assessors (SS, and ANW), Clinicians (MT and SG), other personnel (RD) and statisticians (RMP, AU) were also blinded to the group allocation.

Intervention and Control

After the run-in-period (- 4 weeks), MAD therapy was started on an outpatient basis. Carbohydrate intake was restricted to 20g/day. Detailed MAD protocol, a standard food-exchange list, sample menu, and recipes booklet of standardized recipes including Indian recipe with either 2.5 g or 5 g carbohydrate are provided in eAppendix 2 in the Supplement. High-fat and low-carbohydrate foods were encouraged; however, proteins were unrestricted. The diet was supplemented with multivitamins and minerals. Parents and caregivers were taught to maintain a daily-log of seizure count, meals consumed in a day, dietary intolerance and urine ketones (thrice a day) using colour coded keto-dipsticks. Average ketosis was calculated after 24 weeks of diet. Any adverse effects (i.e. constipation, diarrhoea, weight-loss, anorexia, lethargy, vomiting, sleep, disturbance and hospitalization due to MAD etc.) were noted as per parental/caregivers interview at each visit at 15 days after the diet initiation, 3 months and 6 months. Diet compliance was assessed based on carbohydrate consumption recorded in the daily food-log. Consumption of carbohydrates was calculated by using Diet-Cal software (24). Regular telephonic consultation was given weekly to ensure adherence to the diet.

Control group received a normal diet with no specific dietetic inputs. A trained dietician (MM) provided counselling to the caregivers along with age and weight specific dietary charts based on Recommended Dietary Allowance (RDA) without any carbohydrate restriction. Prescribed ASMs were not changed during the study period in both the groups. The complete blood count and fasting lipid profile at baseline and follow-up at six months were measured. After six months, MAD was offered to those who wanted to follow the therapy.

Outcome measurements

The primary outcome measure was the proportion of patients with greater than 50% seizure reduction (seizure-frequency) from baseline to six months follow-up in both groups. Seizure-frequency was measured as the average seizures/week in the preceding four-week period. Secondary outcome measures included tolerability and adverse-effects of the diet as per parental/caregivers reports. We also compared changes in biochemical parameters, QOL and behaviour from baseline to six months using Quality of Life in Epilepsy for adolescents-48 (QOLIE- AD-48) and Quality of Life in Epilepsy-31 (QOLIE -31) for adults. Both scales contain questions about health related quality of life. Child behaviour checklist (CBCL) and adult behaviour checklist (ABCL) scales were used for the behavioural assessments which were completed by parents/caregiver in each visit. Patients were followed-up and assessed using daily seizure log, food-log, and ketone-log at one month, three months and six months.

Safety

An independent, external data safety monitoring board (DSMB) (acknowledgement section) reviewed all the patient's case-record files periodically for their safety, efficacy and adverse events. We followed DSMB guidelines (25).

Statistical Analysis

Sample size was calculated based on an anticipated decrease of >50% (13), (17) for SDT plus MAD group as compared to SDT group . Expecting a 30% response rate in the intervention arm and 10% in the control arm, power of 80 % and level of significance 5%, a sample size of 144 (72 each group) was calculated. Considering that 10% of patients might be lost to follow-up at six months, 160 patients were enrolled in total.

All Statistical analysis was conducted using STATA (Version 14, Stata Corp; College Station, TX: USA). Variables were checked for normal distribution, and frequency (percentage), mean or median values were used as appropriate. Categorical and continuous variables were computed by $\chi 2$ test/ Fisher-exact and unpaired t-test or Wilcoxon-Mann-Whitney test. Due to skewness, the variables (i.e. SGPT, Triglycerides) were log-transformed and appropriate test applied. Log-binomial regression was used to see the effect of intervention after adjusting the variables which were not comparable at baseline. For the primary outcome, percentage reduction on seizure frequency at six months was analysed using effect size (mean or median difference) with 95% CI, and relative risk (RR with 95% CI) was also analysed to see the risk between the two treatment groups. Intention-to-treat (ITT) analysis was performed by including all patients who were enrolled and assigned to an intervention. Patients who could not be contacted at 6 months and their outcome data were missing; the last observation carried forward (LOCF) method was used for primary and secondary outcomes analysis. Per protocol (PP), analysis was done for patients assigned the allocation and who adhered to the protocol at six months. Effect of diet on seizure-reduction was analysed using worst-case scenario analysis. Adverse effects of the intervention were summarized as number (percentage), and p-value < 0.05 was considered statistically significant.

The study protocol and statistical analysis plan are available in eSAP 1.

RESULTS

Baseline Characteristics

A total of 243 patients with DRE were screened for eligibility between August 2015 to April 2019; 160 patients were enrolled and randomly assigned to the intervention (n=80) or control (n=80) group. Fifty-two patients withdrew from the study, and the remaining 108 patients (46: intervention and 62: control) who completed six months follow-up were included for the per-protocol analysis. The reasons for the patient's withdrawal and exclusion from the study are given in the CONSORT chart (Figure 2).

The demographic and clinical characteristics of the patients were comparable at baseline except for gender (p=0.006) (**Table 1**). Median of the baseline seizures frequency were similar in both groups (intervention-16.5; and control- 24.0; p = 0.88). Most of the patients had epilepsy of structural (MAD -52.5%, SDT -57.5%) or unknown aetiology (MAD-45.0%, SDT 40.0%). Most patients were on at least 4 or more ASMs, the frequent of these being Levetiracetam (MAD-60.0%, SDT-70.0%), Valproate (MAD-75.0%, SDT-75.0%), and Clobazam (MAD-62.5%, SDT-55.0%) (eFigure 2 in the Supplement). Non-vegetarians were higher in both groups (MAD-65.0%, SDT-58.7%) as compared to vegetarians (MAD-35.0%; SDT-41.2%) (eFigure 3).

Urine ketones levels were moderate to high (40-80mg/dl) throughout the study period. The mean morning and evening levels of urine ketosis among the patients in the diet group were 58.3 ± 8.0 mg/dl and 62.2±22.6 mg/dl, respectively, indicating satisfactory adherence to the diet. Baseline demographic and clinical details were performed for adolescents and adults (eTable 1, eTable 2 in the Supplement).

Primary and secondary outcomes

At the end of the study period, the proportion of patients with >50% seizure reduction from baseline was significantly higher in the intervention group (Table 2) as per both ITT [intervention-26.2%; control-2.5%, p value-0.001] and per-protocol analysis (intervention-45.7%; control-3.2%, p-value-0.001). It was also observed that >50% seizure reduction in the intervention group was 10 times more as compared to the control group (RR=10;95% CI 2.54, 43.3, p=0.001). In the intervention

group, 5.0% (ITT analysis) and 8.7% (PP analysis) patients were seizure-free at the end of follow-up, whereas none of the patients were seizure-free in the control group. These differences in seizure freedom rate were statistically significant as per the PP analysis (p=0.03) and the ITT analysis (Table 2). Median (IQR) percentage reduction in seizure frequency from baseline was found to be significant (p=.0.001) in the intervention group [12.4 (-0.94-50.70)] as compared to the control group [0 (-56.08, 9.45)]. On adjusting variables (i.e. gender), there was 13.8 (95% CI 3.1, 62.6; p= 0.001-ITT analysis) and 24.4 (95% CI 5.24, 113.8, p=0.001-PP analysis) times more seizure reduction (>50 %) observed in intervention group as compare to control group. Furthermore, as per ITT analysis, the proportion of adult and adolescent patients having>50% seizure reduction and percentage change in seizure-frequency were significantly higher (p=0.001) in the intervention group as compared to the control group (eFigure4–eFigure7 in the Supplement). As per PP analysis, significant improvement (57.1%; p=0.001) in seizure reduction was most notable in the adult population of the intervention group versus control group (eTable 3 in the Supplement).The worst-case scenario analysis, revealed no significant improvement (>50 % seizure reduction) between the intervention and control group (eTable 4).

There were no significant differences (p>0.05) in the mean scores of body weight, weight loss (eTable 5 in the Supplement) and biochemical profiles between the two groups at six months (Table 3). There was no change in the majority of biochemical parameters at six months on the diet when compared to the baseline in both groups (eFigure 8, A–G). The difference in the QOL and behaviour scores was statistically significant (p=0.0005 and p=0.015 respectively) in the intervention group as compared to the control group at six months (Table 3).

A significant improvement (eTable 6) from baseline was noted in the mean score of QOL (baseline: 52.7±11.6 and last follow-up: 58.7±14.2; p=0.001[adult]; 35.5±14.3 (Baseline) & 45.4±18.3 (follow-up); p=0.001[adolescent]) in the intervention group. No significant difference in QOL from baseline was found in adult subjects of the control group, whereas significant deterioration was

observed in adolescents (baseline: 41.3± 15.0and 6-months follow-up: 33.8± 15.3; p=0.0001). Most of the patients in the intervention group had clinically meaningful increase (6.0 points -adults and ~10 points -adolescents) in their overall QOL.

Total T-scores on CBCL scale indicated lesser behavioural problems among intervention as compared to controls; difference of the mean total behaviour T-score from baseline to follow-up [8.3, p=0.0069 (adult); 3.7, p=0.03 (adolescent)] in the intervention group while in control group [-3.5, p= 0.0179(adult); -0.06, p=0.95 (adolescent)](eTable 7 in the Supplement).

Dietary adherence/ compliance [median percentage (range)] was 91.07 (87.5-92.85) in MAD group at 6 months (eFigure 9, eTable 8 in the Supplement). No significant adverse effects were observed in patients receiving MAD. Although, one patient had weight loss; two patients had diarrhoea (4.3%). The most common adverse effects were constipation, vomiting, diarrhoea, lethargy and anorexia, which resolved by dietary modifications (eTable 9).

This trial was supported by the Centre of Excellence for epilepsy (COE)-Phase-II, which is funded by the Department of Biotechnology, Govt. of India in collaboration with AIIMS, New Delhi and NBRC, Manesar, Gurgaon (Haryana).

DISCUSSION

In this RCT, we investigated the effect of an add-on MAD therapy on seizure-reduction in adolescents and adults with DRE. MAD was found to be more efficacious for reducing seizure frequency than SDT alone. 26.2% of patients had >50 % seizure-reduction in the intervention group compared to the Control group. The result of the present RCT agree with previous findings (13), (15), (21), (16), and the observed seizure reduction was comparable with previously published reports on MAD with DRE (18),(17),(26),(27) which suggest that MAD for DRE in adults and adolescents is well tolerated; however, data on MAD treatment in adults are limited (21),(22).The present cohort demonstrated a lesser reduction in seizure frequency on MAD as compared to another study by Kossoff et al. (17) in adults and in children (13),(15),(16). This difference could be

partially accounted for by the fact that the MAD diet was started late in our clinical setting. In our study, patients had duration of epilepsy of more than ten years on an average and had a median of 37.5 seizures per month in intervention group and 26.5 in control group; after having tried an average of four different ASMs, and most presented with structural (bilateral hypoxic ischemic changes) aetiology.

An RCT done in adults in Iran reported a 35.5% responder (>50% Seizure-reduction) versus no responder in the control group (21). Another study by Kverneland et al could not detect a decrease in seizure frequency (22). Both these studies had relatively low number of participants and a shorter follow-up period.

Our study was conducted in a larger cohort, including adolescents and adults, with a six-month follow-up. On subgroup analysis, >50% seizure reduction was found in 32.5 % of the adult population. Use of exchange list and recipe booklet helped in the initiation of MAD with the flexibility of meal choices and ease of administration. Hence, an ideal treatment option for low resource settings.

On PP analysis, we have found similar efficacy of MAD on seizure reduction (45.7%), which is comparable to the observational study done by Kossoff et. al (10) in contrast to other studies reported by Miranda et al (11) and Zare et al (21). Worst case scenario analysis for the missing data was carried out and we observed that there was no significant difference between intervention and control group for favourable outcome (>50% Seizure reduction) and unfavourable outcome (≤50% Seizure reduction). The analysis was done due to the higher drop-outs in our study(28),(29).

Reduction in seizure frequency and QOL improved significantly for the entire population in adults and adolescents in the intervention group. There was positive trend (correlation) seen between the improvement in QOL and seizure control ($r=0.17$, $p=0.027$) which was significant. The reasons may be probably fewer and lower frequency of seizures that visibly enhanced quality of life. Many

other investigators have reported a better QOL without any standard scales, including recent studies on a diet (30), (31),(32).

Interestingly, we have not found a significant difference in weight loss (>10%) in the diet group, which is supported by previous studies (21), (18). However, weight loss is more common in adults as reported by Kossoff et al (17). In our study, there was no change in majority of biochemical parameters at six months on the diet when compared to the baseline. None of the patients had hyperuricemia. However, one study reported increase in lipid profile over first 3 months of the diet, these values normalized within a year of treatment, including in patients treated with MAD for more than 3 years (33).Longer follow-up data is required to assess the change in the lipid profile in adults on MAD. Other studies have reported some side effects (i.e. Gastrointestinal complaints, dyslipidemias, constipation and weight-loss) (21),(34),(27).Kidney stones(31) are a common diet-induced problem in children in the case of diets. None in our study reported renal stones possibly due to adequate liquid consumption during the dietary intervention. Increased seizure-frequency was reported in one subject. The seizure aggravation in this patient is hard to explain. Others have reported an aggravated seizure frequency when on diet (22),(27).

We found 32.5% dropouts due to lack of efficacy, non-acceptability of diet and inability to follow-up (around covid time). Other reports also show a variation in the dropout rate between 7%-50% (35),(36), (13), (15), (21). We also assessed QOL and behaviour using structural scales in the whole cohort along with diet compliance by an expert dietician (MM) which added strength to our study. Our study has few limitations; blinding could not be done with the individuals and dieticians, as it required close interaction with patients. Due to resource constraints, the behaviour could be assessed only in a subset of patients and not the entire cohort. Compliance to diet is more challenging in long term, especially in adults. However, the tolerance of MAD is much better than high fat diet (Classical KD) (15). Daily-logs maintained by caregivers could have missed some

seizures, including nocturnal seizures, and runs the risk of introducing subjective errors. A multicentric trial including all primary dietary options like KD, MAD and LGIT in older adults with DRE having outcomes of seizure reduction, adverse events and cognitive effects is required to further validate the results. In addition, a selection bias cannot be ruled out because this was a single-centre study.

CONCLUSION

MAD therapy was efficacious, feasible, well-tolerated, with better compliance along with seizure-reduction in adolescents and adults with DRE. Reduction of seizure frequency reflected in the improvement of the quality of life in all patients in the intervention group as compared to the control group. Future studies would be needed to identify neurophysiological and genetic biomarkers associated with MAD response which may have implications for clinical care by encouraging targeted and earlier use of the MAD and also individualized risk-benefit analysis of therapeutic diet, which can provide alternative therapy to standard-care treatment.

WNL-2022-201574_esap1 --http://links.lww.com/WNL/C563

WNL-2022-201574_sup --- http://links.lww.com/WNL/C564

REFERENCES:

1. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy. Neurology. 2011 Sep 6;77(10):1005–12.

2. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069–77.

3. Wiebe S, Jette N. Pharmacoresistance and the role of surgery in difficult to treat epilepsy. Nat Rev Neurol. 2012 Dec;8(12):669–77.

4. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018 May 21;3(2):175–92.

5. Kim JA, Yoon JR, Lee EJ, Lee JS, Kim JT, Kim HD, et al. Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. Epilepsia. 2016 Jan;57(1):51–8.

6. Payne NE, Cross JH, Sander JW, Sisodiya SM. The ketogenic and related diets in adolescents and adults-A review: Ketogenic and Related Diets in Adolescents and Adults. Epilepsia. 2011 Nov;52(11):1941–8.

7. Kossoff EH, Dorward JL. The Modified Atkins Diet. Epilepsia. 2008;49(s8):37–41.

8. Martin-McGill KJ, Jackson CF, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev [Internet]. 2018 Nov 7 [cited 2020 Jul 26];2018(11). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6517043/

9. Liu H, Yang Y, Wang Y, Tang H, Zhang F, Zhang Y, et al. Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies. Epilepsia Open. 2018 Feb 19;3(1):9–17.

10. Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. Epilepsia. 2006 Feb;47(2):421–4.

11. Miranda MJ, Mortensen M, Povlsen JH, Nielsen H, Beniczky S. Danish study of a Modified Atkins diet for medically intractable epilepsy in children: Can we achieve the same results as with the classical ketogenic diet? Seizure - Eur J Epilepsy. 2011 Mar 1;20(2):151–5.

12. Weber S, Mølgaard C, KarenTaudorf, Uldall P. Modified Atkins diet to children and adolescents with medical intractable epilepsy. Seizure - Eur J Epilepsy. 2009 May 1;18(4):237–40.

13. Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: A randomized controlled trial. Epilepsia. 2013;54(3):481–6.

14. Rezaei S, Abdurahman AA, Saghazadeh A, Badv RS, Mahmoudi M. Short-term and long-term efficacy of classical ketogenic diet and modified Atkins diet in children and adolescents with epilepsy: A systematic review and meta-analysis. Nutr Neurosci. 2019 May;22(5):317–34.

15. Sharma S, Goel S, Jain P, Agarwala A, Aneja S. Evaluation of a simplified modified Atkins diet for use by parents with low levels of literacy in children with refractory epilepsy: A randomized controlled trial. Epilepsy Res. 2016 Nov 1;127:152–9.

16. Sondhi V, Agarwala A, Pandey RM, Chakrabarty B, Jauhari P, Lodha R, et al. Efficacy of Ketogenic Diet, Modified Atkins Diet, and Low Glycemic Index Therapy Diet Among Children With Drug-Resistant Epilepsy: A Randomized Clinical Trial. JAMA Pediatr. 2020 Oct 1;174(10):944–51.

17. Kossoff EH, Rowley H, Sinha SR, Vining EPG. A prospective study of the modified Atkins diet for intractable epilepsy in adults. Epilepsia. 2008 Feb;49(2):316–9.

18. Smith M, Politzer N, MacGarvie D, McAndrews MP, Campo M del. Efficacy and tolerability of the Modified Atkins Diet in adults with pharmacoresistant epilepsy: A prospective observational study. Epilepsia. 2011;52(4):775–80.

19. Ye F, Li XJ, Jiang WL, Sun HB, Liu J. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. J Clin Neurol Seoul Korea. 2015 Jan;11(1):26–31.

20. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev [Internet]. 2020 [cited 2021 Mar 25];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001903.pub5/abstract

21. Zare M, Okhovat AA, Esmaillzadeh A, Mehvari J, Najafi MR, Saadatnia M. Modified Atkins diet in adult with refractory epilepsy: A controlled randomized clinical trial. Iran J Neurol. 2017 Apr 4;16(2):72–7.

22. Kverneland M, Molteberg E, Iversen P, Veierød M, Taubøll E, Selmer K, et al. Effect of modified Atkins diet in adults with drug-resistant focal epilepsy: A randomized clinical trial. Epilepsia. 2018 Jun 1;59.

23. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 23;340:c332.

24. DietCal [Internet]. [cited 2021 Jul 19]. Available from: http://dietcal.in/

25. Data and Safety Monitoring Board (DSMB) Guidelines [Internet]. [cited 2022 Aug 9]. Available from: https://www.nidcr.nih.gov/research/human-subjects-research/toolkit-and-education-materials/interventional-studies/data-and-safety-monitoring-board-guidelines

26. Green S, Nguyen P, Kaalund-Hansen K, Rajakulendran S, Murphy E. Effectiveness, retention, and safety of modified ketogenic diet in adults with epilepsy at a tertiary-care centre in the UK. J Neurol. 2020 Apr 1;267.

27. Cervenka MC, Terao NN, Bosarge JL, Henry BJ, Klees AA, Morrison PF, et al. E-mail management of the Modified Atkins Diet for adults with epilepsy is feasible and effective. Epilepsia. 2012;53(4):728–32.

28. Mavridis D, Chaimani A, Efthimiou O, Leucht S, Salanti G. Addressing missing outcome data in meta-analysis. Evid Based Ment Health. 2014 Jul 9;17.

29. Vibha D, Prasad K. How to Deal with Missing Data? Neurol India. 2020 Jul 1;68(4):886.

30. Roehl K, Falco-Walter J, Ouyang B, Balabanov A. Modified ketogenic diets in adults with refractory epilepsy: Efficacious improvements in seizure frequency, seizure severity, and quality of life. Epilepsy Behav EB. 2019;93:113–8.

31. Kverneland M, Selmer KK, Nakken KO, Iversen PO, Taubøll E. A prospective study of the modified Atkins diet for adults with idiopathic generalized epilepsy. Epilepsy Behav. 2015 Dec 1;53:197–201.

32. Bruce S, Devlin A, Air L, Cook L. Changes in quality of life as a result of ketogenic diet therapy: A new approach to assessment with the potential for positive therapeutic effects. Epilepsy Behav EB. 2017 Jan;66:100–4.

33. Cervenka MC, Patton K, Eloyan A, Henry B, Kossoff EH. The impact of the modified Atkins diet on lipid profiles in adults with epilepsy. Nutr Neurosci. 2016 Mar 15;19(3):131–7.

34. Kossoff E, Rowley H, Sinha S, Vining E. A Prospective Study of the Modified Atkins Diet for Intractable Epilepsy in Adults. Epilepsia. 2008 Feb 1;49:316–9.

35. El-Rashidy OF, Nassar MF, Abdel-Hamid IA, Shatla RH, Abdel-Hamid MH, Gabr SS, et al. Modified Atkins diet vs classic ketogenic formula in intractable epilepsy. Acta Neurol Scand. 2013 Dec;128(6):402–8.

36. Kossoff EH, Turner Z, Bluml RM, Pyzik PL, Vining EPG. A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet. Epilepsy Behav. 2007 May 1;10(3):432–6.

Table 1: Baseline Demographic and Clinical Details of All Subjects with DRE

Baseline Characteristics	**Intervention group (n=80)**	**Control group (n=80)**	**p-value**
Age at enrolment (in years)*	19.5 ±7.4	19.4 ±7.1	0.92
Gender n(%) • Male • Female	 64 (80) 16 (20)	 48 (60) 32 (40)	0.006
Weight (in kg)	58.9 ±19.8	59.6± 19.9	0.81
BMI(Kg/m2)	22.5 ±5.8	23.5 ±6.2	0.28
Age at first seizure (in year) [Median (IQR)]	5.5 (2.0-8.5)	6.5 (3-10)	0.28
Duration of epilepsy (in year)*	12.9 ±6.3	11.7 ±5.7	0.24
Number of seizures per month [Median (IQR)]	37.5 (11.0-75.0)	26.5 (6.5-72.5)	0.10

No of ASMs tried in the past months median (mean±SD)*	4 (4.0 ±0.9)	4 (4.1±0.9)	0.86
Seizure Type (%) • Tonic • Atonic • Focal seizures • Generalized Tonic-Clonic Seizures • Myoclonic jerks • Multiple seizure types	 2(2.5) 3 (3.7) 33(41.3) 27(33.7) 10(12.5) 5 (6.3)	 5 (6.3) 1(1.2) 43 (53.8) 23(28.7) 5(6.3) 3 (3.7)	0.31
Etiology n (%) • Structural • Infectious • Unknown	 42 (52.5) 2 (2.5) 36 (45.0)	 46 (57.5) 2 (2.5) 32 (40.0)	0.86
Levels of biochemical parameters*			
Uric Acid, µmol/L	4.3 ±1.4	4.3 ±1.3	0.99
SGOT, mmol/L	26.7 ±9.9	26.1 ±8.3	0.93
SGPT, mmol/L	30.6 ±18.6	26.1 ±10.5	0.13
Total cholesterol, mmol/L	170.0 ±41.5	171.7 ±40.5	0.79
LDL, mmol/L	103.3±36.4	105.3 ±35.6	0.73
HDL, mmol/L	49.7 ±10.4	47.8 ±16.5	0.39
Triglycerides, mmol/L	106.9 ±54.3	115.4±52.2	0.18
Quality of life*	44.1±15.6	46.7±15.2	0.29

Behavior problems (T- scores)* (n=49)	71.2±6.3 (n=23)	69.8±9.1 (n=26)	0.56

(Data are represented as *=Mean ± SD; IQR=interquartile range; Intervention group (Standard drug therapy (SDT) plus Modified Atkins Diet (MAD);control group (SDT-alone), ; ASMs=Anti-seizure Medications, BMI- body mass index; LDL=Low-density lipoproteins; HDL= High-density lipoproteins; SGOT= Serum glutamic-oxaloacetic transaminase; SGPT= Serum glutamic pyruvic transaminase).

Table 2: Efficacy of diet in Seizure frequency at the end of treatment (6 months) in all patients

Seizure Reduction	**Intervention Group**	**Control Group**	**Proportion Difference (95%CI)**	**RR (95% CI)**	**P-value**
A) Intention–to-treat(ITT) analysis [SDT plus MAD group (n=80) and SDT group (n=80)]					
• [$]More than 50 % • More than 90% • Complete seizure-free	21 (26.2%) 6 (7.5%) 4 (5%)	2 (2.5%) 0 0	23.7 (13.5,33.9) 7.5 (1.7, 13.3) 5.0 (0.2, 9.7)	10 (2.54, 43.3) Undefined Undefined	<0.001** 0.028* 0.116
B) Per-Protocol (PP) analysis [SDT plus MAD group (n=46) and SDT group (n=62)]					
• **[$]More than 50 %** • More than 90% • Complete seizure-	**21(45.7%)** 6 (13%) 4 (8.7%)	**2 (3.2%)** 0 0	**42 .0(27.3, 57.4)** 13 (3.3, 22.7) 8.7(0.5, 16.8)	**14.2 (3.94,57.35)** - -	**<0.001**** 0.005* 0.03*

free					

Intervention group [Standard drug therapy (SDT) plus Modified Atkins Diet (MAD)]; control group (SDT-alone), RR=relative risk **=P value<0.005, *=P<0.05, **$=**Primary outcome > 50% seizure reduction)

Table 3: Treatment effects at the end of the 6 months in the all patients

Outcome	**Intervention group (n=80)**	**Control group (n=80)**	**Difference (95% CI)**	**p-value**
BMI(kg/m2)	22.5±5.3	23.6±5.8	-1.13 (-2.86, 0.60)	0.19
Body weight (kg)	58.8±18.5	59.9±18.8	-1.10(-6.94, 5.46)	0.70
Weight loss[$]	1.9±0.1	1.9 ± 0.1	-0.01 (-0.05, 0.03)	0.56
Uric Acid, µ mol/L	4.6±1.5	4.3±1.4	0.35 (-0.11, 0.80)	0.13
SGOT, mmol/L	27.5±11.6	27.0±10.5	0.62 (-2.22, 3.47)	0.66*
SGPT, mmol/L	33.8±25.3	28.5±16.5	5.34(-1.34, 12.02)	0.13*
Total cholesterol, mmol/L	177.3±35.3	173.6±37.1	3.73(-7.56, 15.04)	0.51
LDL, mmol/L	110.4±34.0	108.0±29.8	2.37(-7.62, 12.36)	0.63
HDL, mmol/L	50.5±14.2	49.4±15.0	1.06 (-3.49, 5.63)	0.64
Triglycerides, mmol/L	108.3±58.1	112.1±45.4	-3.81(-20.10, 12.46)	0.19

Quality of life	52.1±17.6	42.5±16.4	9.59 (4.26,14.92)	**0.0005*****
Behaviour Problems (T-scores)	65.6±7.9	71.4±8.1	-5.77 (-10.39, -1.16)	**0.015****

(Data represented as Mean ±SD; Intervention group [Standard drug therapy (SDT) plus Modified Atkins Diet (MAD)]; control group (SDT-alone), ; BMI=Body Mass Index; SGOT= Serum glutamic oxaloacetic transaminase; SGPT= Serum glutamic pyruvic transaminase; LDL= Low-density lipoproteins; HDL= High-density lipoproteins; * p- value given using non –parametric test; ** p- value <0.05, *** p-value<0.0005, $=categorical variables

Figure 1 : Study Flowchart

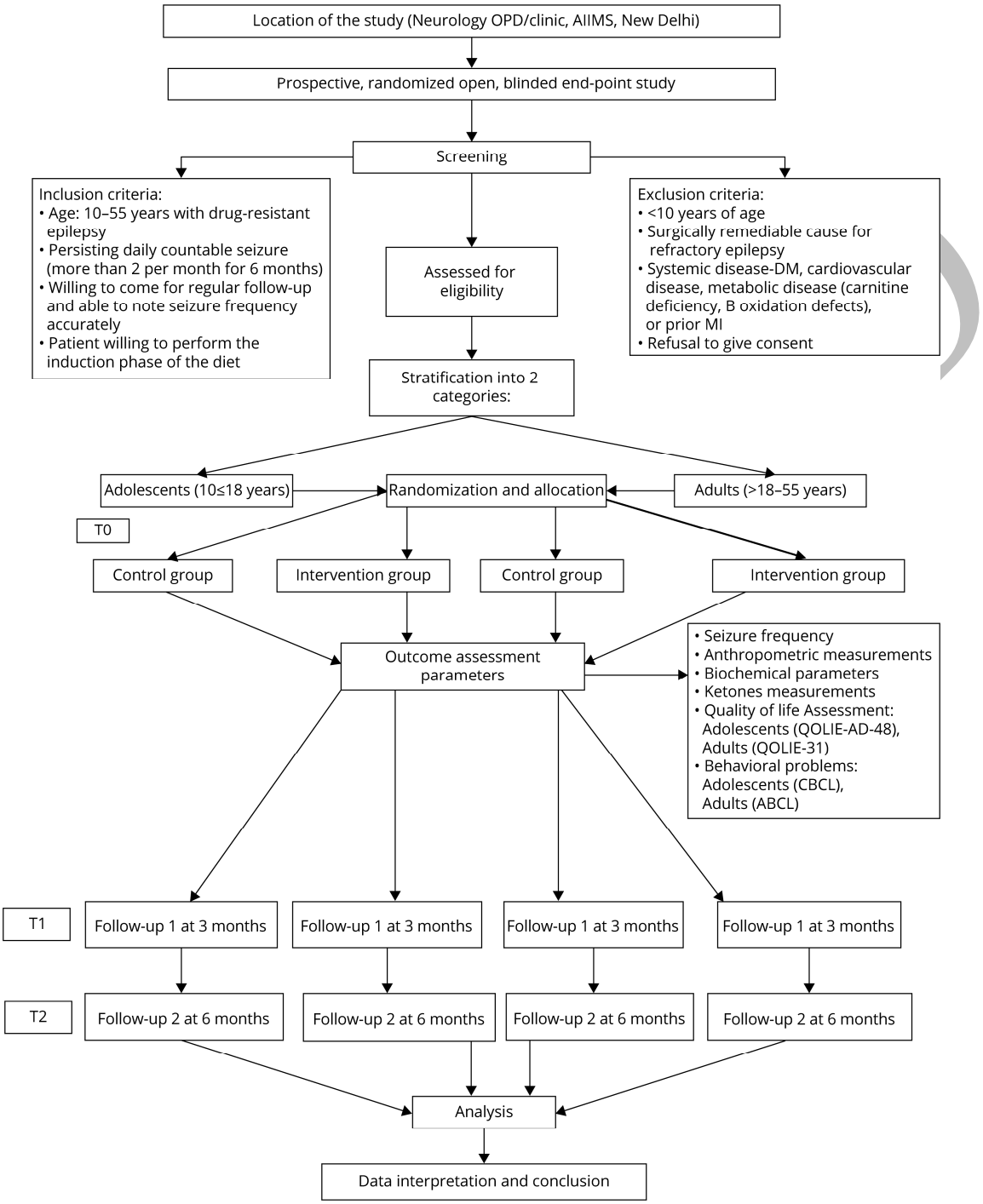
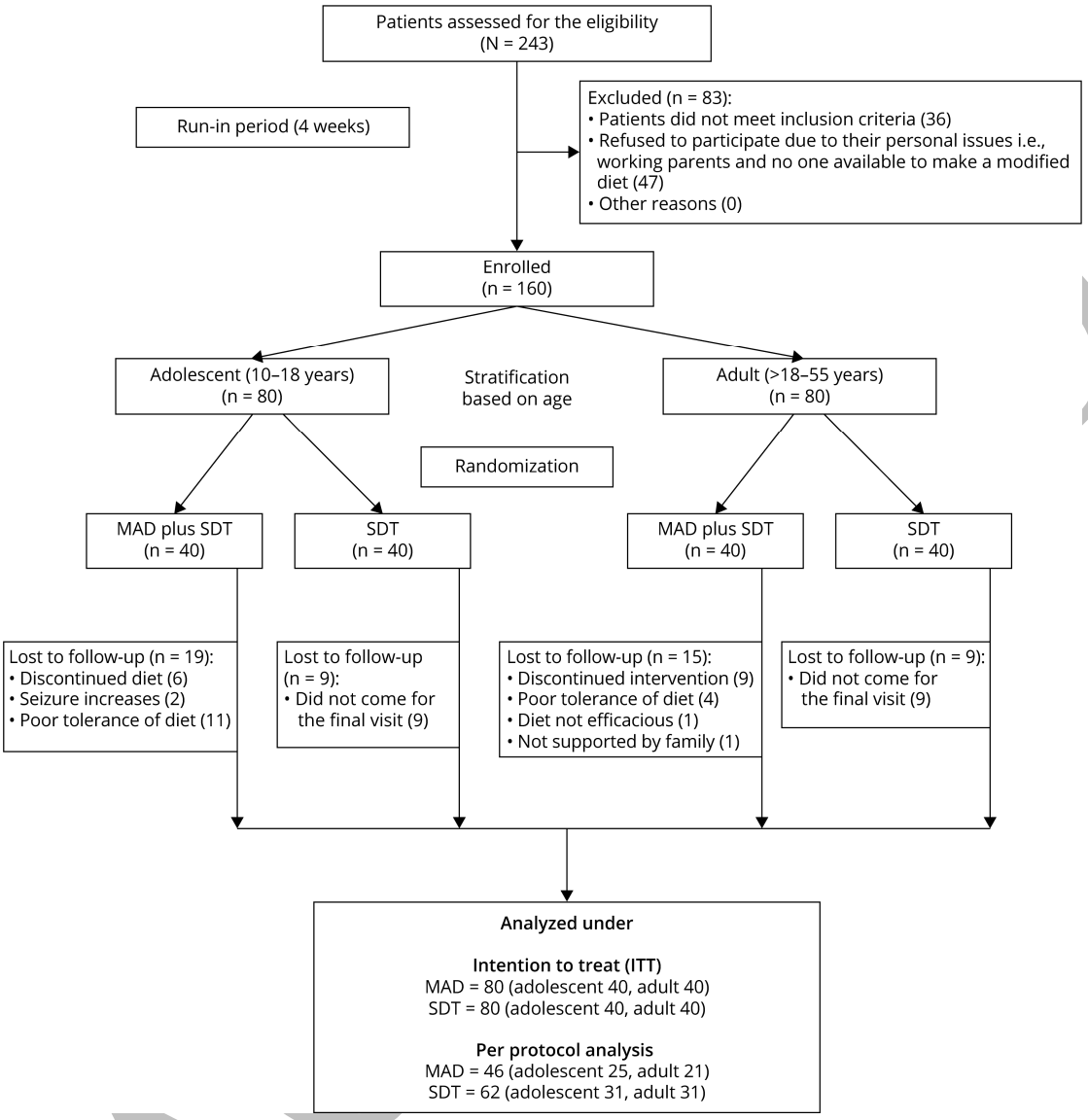


Figure 2: CONSORT flow chart of the study.



Safety, Efficacy, and Tolerability of Modified Atkins Diet in Persons With Drug-Resistant Epilepsy: A Randomized Controlled Trial

Mala Manral, Rekha Dwivedi, Sheffali Gulati, et al.

Neurology published online January 4, 2023
DOI 10.1212/WNL.0000000000206776