



# Keto Is Not Just for Kids: A Randomized Trial of a Modified Atkins Diet for Adolescents and Adults With Anti-Seizure Medication-Resistant Epilepsy

Epilepsy Currents  
2023, Vol. 23(3) 147-149  
© The Author(s) 2023  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/15357597231157488  
journals.sagepub.com/home/epi



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

Manral M, Dwivedi R, Gulati S, Kaur K, Nehra A, Pandey RM, Upadhyay AD, Sapra S, Tripathi M. *Neurology*. 2023. doi:10.1212/WNL.000000000206776

**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 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  $52.1 \pm 17.6$  in the intervention group versus  $42.5 \pm 16.4$  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 ( $65.6 \pm 7.9$  versus  $71.4 \pm 8.1$ ,  $p = 0.015$ ) 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.

## Commentary

Fun fact—ketogenic diet therapies have been used to treat epilepsy in patients of all ages for over one century.<sup>1</sup> In the original article published by R.M. Wilder in 1921 entitled “High fat diets in epilepsy,” the author presented 3 cases of patients ages 13, 23, and 31 years who responded to a ketogenic diet for the treatment of epilepsy. This was described as a high-fat diet which produced ketone bodies through fat metabolism, resulting in a state of ketosis (not to be confused with ketoacidosis) while providing adequate nutrition. This was a novel approach proposed to replace fasting which was previously used as a management strategy for epilepsy. The author

described fasting as “brutal” by comparison. This original study was followed up by another in 1930 examining response to a ketogenic diet in 100 adolescents and adults and the majority were found to derive benefit.<sup>2</sup> While ketogenic diet therapies, also known as ketogenic diets or ketogenic therapies were not used extensively for several decades to follow,<sup>3</sup> they re-emerged in the late 1900s, primarily in the treatment of children and adolescents with severe anti-seizure medication-resistant seizure disorders and certain rare epilepsy syndromes.<sup>4</sup> Within the last decade, experience treating larger numbers of adults with ketogenic diet therapies for epilepsy have been reported<sup>5,6</sup> and more recently, small studies that randomized adults to a



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).



modified Atkins diet versus standard-of-care treatment.<sup>7,8</sup> A modified Atkins diet (MAD) limits carbohydrate consumption while increasing fat with adequate protein and is not as restrictive as the “classic” ketogenic diet originally proposed in the 1920s. Study results were conflicting such that one study found that 35% of adults on MAD showed a >50% seizure reduction at 2 months,<sup>8</sup> while the other study showed only a moderate benefit (>25% seizure reduction) at 12 weeks.<sup>7</sup> In a recent Cochrane review,<sup>9</sup> the authors concluded that further research is needed to support the use of ketogenic diet therapies in adults with anti-seizure medication-resistant epilepsy.

Due to conflicting study findings and also lack of awareness in the medical community regarding use of ketogenic diet therapies for adults with epilepsy, there remains a great deal of skepticism from many adult neurologists regarding whether or not to recommend diet interventions to their patients. Some actively dissuade their patients from attempting ketogenic diet therapies, stating that they are too difficult for adults to follow, are ineffective, or cause an undue burden and resultant decline in quality of life. Because of the recent emergence of the “keto craze” for weight loss in adults, other clinicians may have heard anecdotal reports or have personal experience with side effects, which occur most often when individuals on these diets are not closely monitored by medical professionals including clinicians and dietitians familiar with ketogenic diet therapies.

In a study recently published in *Neurology*, Manral and colleagues<sup>10</sup> performed a randomized controlled trial at a tertiary care center in New Delhi, India, of 80 adolescents (ages 10 to less than 18 years) and 80 adults (18-55 years) with anti-seizure medication-resistant epilepsy, randomized to a MAD as an adjunct to standard-of-care anti-seizure medication management (active intervention arm) versus standard care alone (control arm). Both groups received dietitian support including counseling on how to follow MAD in the active arm (high fat, carbohydrate intake limited to 20 grams or fewer per day and unlimited protein) or Recommended Daily Allowances of macronutrients in the control group. Anti-seizure medications remained unchanged for the study period of 6 months.


The retention rate was 58% in the active arm compared to 78% in the control arm which is comparable to prior studies in adults.<sup>6</sup> Using an intention-to-treat analysis, there was a significant reduction in seizure frequency in the intervention arm compared to the control arm as well as improvement in quality of life and behavioral measures at 6 months. One quarter of patients had >50% seizure reduction in the intervention arm compared to fewer than 3% in the control arm. Five percent of participants in the intervention arm became seizure-free compared to none in the control arm, which did not reach statistical significance.

One major finding to highlight from this study with regard to the role of ketogenic diet therapy in the management of adults with anti-seizure medication-resistant epilepsy is that in a sub-analysis, the reduction in seizure frequency was significantly higher for adult patients in the intervention arm (57%) compared to adolescents. Prior studies focused primarily on

children and adolescents but have not made this direct comparison. In addition, the finding that quality of life improved overall in the intervention arm compared to the control arm contradicts prior assumptions that the MAD is burdensome. Side effects were also rare.

Limitations are inherent in diet research, most notably the challenges that arise with blinding participants to their assigned treatment arm given that they are aware of the dietary counseling that they receive and resultant changes to the foods that they consume as well as potential social, and economic impacts and increased time needed to prepare meals. This study attempted to address this challenge by providing dietitian support to participants in the control arm in addition to the intervention arm including counseling regarding healthy macronutrient consumption. Another limitation was that this study focused on a single ketogenic diet therapy, the MAD, so broader statements cannot be made regarding efficacy of other ketogenic diet therapies such as the classic ketogenic diet in management of adolescent and adult epilepsy.

Overall, this study supports the use of a MAD in the management of uncontrolled seizures in adolescents and adults with anti-seizure medication-resistant epilepsy and indeed shows that adults may benefit even more from this intervention than adolescents. The study also followed participants for 6 months, showing that the diet can be followed long-term with improvement in quality of life and minimal side effects when appropriately used. Therefore, consideration should be made to offering this option to adults whose seizures have not responded to anti-seizure medications and who are not epilepsy surgery candidates or prepared to undergo surgical evaluation. The role of ketogenic diet therapies versus new anti-seizure medications and neuromodulation devices or which diet is most feasible, safe, and effective for adults has not yet been explored. Now that this study has provided definitive evidence that a MAD is effective in adults with anti-seizure medication-resistant epilepsy, important next steps will be to explore whether long-term side effects such as hyperlipidemia and reduced bone mass as well as risks of teratogenicity are potential concerns.

Mackenzie C. Cervenka, MD   
Johns Hopkins Medicine

#### ORCID iD

Mackenzie C. Cervenka  <https://orcid.org/0000-0002-4760-857X>

#### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Dr Cervenka receives or has received research grants from VitaFlo, a business unit of Nestlé Health Science, Nutricia, a part of Danone, Glut1 Deficiency Foundation, and BrightFocus Foundation. Honoraria from Nutricia/Danone, VitaFlo/Nestlé Health Science, and The Neurology Center Rockville. Royalties from Demos/Springer Publishing Company. Consulting for Nutricia/Danone and Glut1 Deficiency Foundation.



## References

1. Wilder RM. *The Effects of Ketonemia on the Course of Epilepsy*. Mayo Clinic Proceedings. 1921;2:307-308.
2. Barborika C. Epilepsy in adults: results of treatment by ketogenic diet in one hundred cases. *Arch Neurol*. 1930;6:904-914.
3. Catenaccio E, Bergin AM, Pinto AL, Nickels K, Kossoff EH. The role of mentorship and collaboration in the fall and rebirth of the ketogenic diet. *Pediatr Neurol*. 2021;119:11-14.
4. Kossoff EH, Zupec Kania BA, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open*. 2018;3(2):175-192.
5. Cervenka MC, Henry BJ, Felton EA, Patton K, Kossoff EH. Establishing an adult epilepsy diet center: experience, efficacy and challenges. *Epilepsy Behav*. 2016;58:61-68.
6. Klein P, Tyrlikova I, Mathews GC. Dietary treatment in adults with refractory epilepsy: a review. *Neurology*. 2014;83(21):1978-1985.
7. Kverneland M, Molteberg E, Iversen PO. Effect of modified Atkins diet in adults with drug-resistant focal epilepsy: a randomized clinical trial. *Epilepsia*. 2018;59(8):1567-1576.
8. Zare M, Okhovat AA, Esmailzadeh A, Mehvari J, Najafi MR, Saadatnia M. Modified Atkins diet in adult with refractory epilepsy: a controlled randomized clinical trial. *Iran J Neurol*. 2017;16(2):72-77.
9. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database Syst Rev*. 2020;11(11):CD001903.
10. Manral M, Dwivedi R, Gulati S, et al. Safety, efficacy, and tolerability of modified Atkins diet in persons with drug-resistant epilepsy: a randomized controlled trial. *Neurology*. 2023. doi:10.1212/WNL.0000000000206776