



## ORIGINAL ARTICLE

# Prospective study of the modified Atkins diet in adult drug-resistant epilepsy: effectiveness, tolerability, and adherence

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Received 17 March 2021; accepted 17 October 2021

Available online 28 April 2023

## KEYWORDS

Modified Atkins diet;  
Drug-resistant  
epilepsy;  
Adult

## Abstract

**Introduction:** Drug-resistant epilepsy presents high worldwide prevalence and is difficult to control despite the wide variety of available antiepileptic drugs (AED). The modified Atkins diet (MAD) is an additional treatment alternative. Several studies have addressed the use of the ketogenic diet and MAD in children with drug-resistant epilepsy, but insufficient research has been conducted into adults with the same condition.

**Objective:** To evaluate the effectiveness and tolerability of, and adherence to, the MAD in adults with drug-resistant epilepsy.

**Material and methods:** We conducted a 6-month pre-post prospective study at a reference hospital. Patients were prescribed the MAD with limited carbohydrate intake and unlimited fat intake. We conducted clinical and electroencephalographic follow-up according to the relevant guidelines, and assessed adverse effects changes in laboratory findings, and adherence.

**Results:** Thirty-two patients with drug-resistant epilepsy were included in the study. Patients' mean age was 30 years, mean disease progression time was 22 years, and all patients had focal or multifocal epilepsy. Thirty-four percent of patients presented > 50% decreases in overall seizure frequency ( $P = .001$ ); seizure control was greater in the first month and subsequently declined. These patients presented weight loss (RR: 7.2; 95%

DOI of refers to article: <https://doi.org/10.1016/j.nrl.2021.10.009>.

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<https://doi.org/10.1016/j.nrleng.2021.10.008>

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CI, 1.3–39.5;  $P = .02$ ), good to fair adherence only in the first and third months (RR: 9.4; 95% CI, 0.9–93.6;  $P = .04$  and RR: 0.4; 95% CI, 0.30–0.69;  $P = .02$ , respectively). Tolerability data showed that the MAD is safe: adverse effects were minor and short-lived in most cases, with the exception of mild to moderate hyperlipidaemia in one-third of patients. The adherence rate was 50% at the end of the study.

**Conclusions:** In adults with drug-resistant focal epilepsy, the MAD showed adequate tolerability and moderate but decreasing effectiveness and adherence, probably due to a preference for a carbohydrate-based diet.

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## PALABRAS CLAVE

Dieta Atkins modificada;  
Epilepsia farmacorresistente;  
Adulto

## Estudio prospectivo de dieta Atkins modificada en epilepsia farmacorresistente de adultos: efectividad, tolerabilidad y adherencia

### Resumen

**Introducción:** La epilepsia farmacorresistente (EFR) tiene una elevada prevalencia mundial y dificultad en su control pese a una gran variedad de fármacos antiepilépticos (FAE). La Dieta Atkins Modificada (DAM) constituye una alternativa favorable adicional. Existen varios estudios sobre niños con EFR y uso de dieta cetogénica o DAM, pero insuficientes en adultos con la misma condición.

**Objetivo:** Evaluar la efectividad, tolerabilidad y adherencia de la DAM en adultos con EFR.

**Material y métodos:** Estudio prospectivo, antes-después, aplicado por 6 meses en un hospital de referencia. Se instala DAM con limitación de carbohidratos y libertad de dieta grasa. Se realiza un seguimiento clínico y electroencefalográfico con guías relacionadas, además de valorar los efectos adversos, las modificaciones laboratoriales y aplicar un test de adherencia.

**Resultados:** Se incluyeron 32 pacientes con EFR. La edad media fue de 30 años, el tiempo promedio de evolución fue de 22 años y todos tenían epilepsia focal o multifocal. La disminución global de crisis epilépticas  $> 50\%$  se presentó en el 34% de casos ( $P = 0.001$ ); el control fue mayor en el primer mes y decayó posteriormente. Dichos pacientes manifestaron pérdida ponderal (RR 7.2, IC 95% 1.3–39.5;  $P = 0.02$ ), adherencia buena a regular solo en el primer y tercer mes (RR 9.4, IC 95% 0.9–93.6;  $P = 0.04$ ; RR 0.4, IC 95% 0.30–0.69;  $P = 0.02$  respectivamente). La tolerabilidad de DAM se mostró como un tratamiento seguro, dados los efectos adversos menores y de corta duración, en la mayoría, salvo la presencia de hiperlipidemia leve a moderada en un tercio de casos. El test de adherencia mostró 50% de cumplimiento al final del estudio.

**Conclusiones:** La DAM demuestra en adultos con EFR focal una *tolerabilidad* adecuada, una *efectividad* y adherencia moderadas, pero decrecientes, que se atribuyen probablemente debido a la preferencia por una dieta basada en carbohidratos.

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## Introduction

Drug-resistant epilepsy (DRE) affects almost 25% of the population with epilepsy,<sup>1</sup> and is defined as failure of adequate trials of 2 tolerated, appropriately chosen and used antiepileptic drug schedules, whether as monotherapy or in combination, to achieve sustained seizure freedom.<sup>2</sup>

Many patients visit reference hospitals to try to control or decrease the frequency of epileptic seizures. In addition to rational polytherapy and epilepsy surgery, other alternatives have been proposed, including the modified Atkins diet (MAD),<sup>3</sup> based on the same physiological theory as the ketogenic diet, which aims to achieve an anticonvulsant effect through ketosis.<sup>4,5</sup>

Secondary effects of ketosis include nausea, headache, diarrhoea, kidney stones, constipation, weight loss, hyperlipidaemia, hypoglycaemia, and hypocalcaemia, among others. All of these are reversible and mild with MAD.<sup>6,7</sup>

Ketogenic and similar diets are contraindicated in patients with lipid metabolism disorders or who require a carbohydrate-rich diet.<sup>8</sup>

MAD is preferable over the ketogenic diet because it may be followed on an outpatient basis and is more flexible with regard to the intake of carbohydrates (from 10% to 20%) and calories (proteins, 20%–30%; and fats, 60%–70%).<sup>3,9</sup>

The ketogenic diet has been used for almost a century,<sup>10</sup> but was abandoned from the second half of the 20th century due to the appearance of antiepileptic drugs (AEDs) and other less restrictive diet options, including MAD, which was successfully rediscovered in the past 2 decades in children with DRE.<sup>11–13</sup> Results in adults are not uniform, and its use is limited.<sup>14–17</sup>

This study aims to assess the effectiveness, tolerability, and adherence to the MAD to decrease and better control seizures in adult patients with DRE.

**Table 1** Huttenlocher and Panico criteria.

Huttenlocher clinical criteria		Panico electroencephalographic criteria	
1. Excellent control	100% seizure-free	1. Normalisation	Good baseline status with no focal or paroxysmal signs
2. Very good control	> 90% seizure control	2. Significant improvement	Absence of paroxysmal signs, but with focal signs
3. Good control	50%-90% seizure control		
4. Moderate control	< 50% seizure control	3. Mild improvement	Improved organisation, but with occasional general and focal paroxysmal signs persisting
5. Control with no effects	0% with no change in seizures	4. No changes	Same EEG pattern as before
6. Negative effect	Seizure exacerbation	5. Worsening	Worsening in the EEG

## Material and methods

We conducted a prospective intervention study at the reference hospital Centro Médico Nacional de Occidente (Jalisco, Mexico). The study period was 1 March to 1 September 2018.

We included patients aged  $\geq 18$  years meeting diagnostic criteria for DRE and who gave written informed consent to participate. Exclusion criteria included status epilepticus or alternative treatments (surgical or diet-based) in the past 6 months; genetic diseases or lipid metabolism disorders; progressive or fatal neurological diseases; severe comorbidities (kidney stones, kidney failure, heart failure, end-stage liver disease, acute leukaemia, severe systemic lupus erythematosus), body mass index  $< 18$ , pregnancy, and hyperlipidaemia ( $> 190$  mg/dL).

We clearly established the concepts of effectiveness,<sup>18</sup> tolerability,<sup>19–21</sup> and adherence,<sup>22,23</sup> and used the clinical parameters defined by Huttenlocher<sup>24</sup> and the EEG criteria established by Panico<sup>25</sup> to assess the response to ketogenic therapy (Table 1). Lastly, we administered the Morisky-Green adherence test,<sup>26</sup> to assess adherence to the MAD.

### Composition of the modified Atkins diet

The diet recommends taking 3 regular-sized meals or up to 5 smaller meals each day; 15–20 g of carbohydrates daily, unlimited fats (better from plant than animal sources) and moderate levels of proteins which should be combined (variety of meat and fish, eggs, olive oil, cheese, cream, butter, and mayonnaise without limit); leafy green vegetables and low-sugar fruits should be prioritised, with nuts and seeds to be avoided during the first weeks; products derived from refined sugar and white flour should also be avoided.<sup>3,14</sup>

### Procedure

We invited patients to a meeting to inform them about the plans, risks (adverse reactions), and benefits. Patients who agreed to participate signed informed consent forms. They were given a seizure calendar, a telephone number to resolve problems, and a notepad to record any adverse events. Visits were scheduled at months 1, 3, and 6 to monitor body weight, according to changes of more or less than 5 kg; the response to ketogenic therapy, by applying operational clinical and electroencephalographic criteria; and laboratory parameters (complete blood count, glucose, creatinine, urea, sodium, potassium, calcium, magnesium,

transaminases, amylase, and lipase). All participants received daily supplementation with vitamins and calcium. Treatment with AEDs remained unchanged in the following months, unless changes were required.

The MAD was supervised by a nutritionist, who approved the adaptation of foods to the Mexican cuisine. The diet was followed on an outpatient basis. Greater restriction of carbohydrate intake was recommended during the first week. We also recommended partially limited water intake, under supervision (from 750 to 1500 mL per day, although most patients already drank that amount), as well as an intake of 1600–1800 kcal/day in women and 1800–2000 kcal/day in men.

### Effectiveness of the modified Atkins diet

We assessed the frequency of seizures using the seizure calendar, and used the Huttenlocher scale to assess the clinical ketogenic response and the Panico scale for EEG assessment.

### Modified Atkins diet tolerability

At each visit, we monitored adverse reactions in laboratory parameters, clinical adverse reactions (symptoms and weight changes), and the degree of severity (mild, when patients did not need to go to the emergency department; moderate, if they were not hospitalised; and severe, if they were hospitalised).

### Adherence to the modified Atkins diet

All patients presented good adherence to previous medications and had a supportive family network. At each visit, patients were asked about their desire to continue participating in the study, and about the use and convenience of the diet. As possible adherence responses, we defined: high, when they fully adhered to the diet (7/7 days, 100%), moderate, when they frequently adhered to the diet (4–5/7 days, 50%–70%), or low, when they rarely adhered to the diet (less than 2/7 days, lower than 30%). At the end of the protocol, we administered the Morisky-Green adherence test.

### Statistical analysis

We performed a descriptive analysis using frequencies, percentages, and measures of central tendency and dispersion. The chi-square test was applied for qualitative variables, and the *t* test

**Table 2** Frequency of seizures.

Epileptic seizures	Mean	Range	* <i>P</i>
Baseline	30	3–280	
1st month	13	0–80	.017
3rd month	15	0–120	.015
6th month	17	1–140	.020

\* *t* test.

for quantitative variables; the Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. We also calculated the relative risk (RR) and 95% confidence intervals (95% CI). Statistical significance was set at  $P < .05$ . Data were analysed using the SPSS statistical software, version 24.0 (SPSS Inc.; Chicago, IL, USA).

To assess the effectiveness of MAD in reducing seizure frequency, we calculated the absolute risk reduction, reduction in RR, and the number needed to treat.

### Ethical considerations

The study complies with the principles of the Declaration of Helsinki and Mexican healthcare regulations. The Hospital Research Ethics Committee approved the protocol, with record number 2016/1301/72; it was also recorded in ClinicalTrials.gov (identifier: NCT03183076).

### Results

A total of 50 patients with DRE were invited to participate; 32 of them accepted, of whom 19 (59%) were women and 13 (41%) men. Mean age (standard deviation) was 30 (10.3) years (range, 17–55) and mean disease progression time was 21.6 (10.3) years (range, 6–51).

All cases presented focal or multifocal DRE, with no cases of idiopathic or unknown-onset epilepsy. Seizures were motor in 19 (59.4%) and non-motor in 13 (40.6%). Thirty patients received 3 or more AEDs (93.7%).

Epilepsy aetiology was acute symptomatic in 11 patients (34.3%) and remote symptomatic in 21 (65.6%).

Most patients presented no comorbidities, with the exception of 5 presenting migraine ( $n = 1$ ), arterial hypertension ( $n = 1$ ), hypothyroidism ( $n = 2$ ), and liver disease ( $n = 1$ ), all under treatment.

### Effectiveness of the modified Atkins diet

The monthly average seizure frequency before starting the diet was 30 per month, with a maximum decrease in the first month on the diet and a subsequent progressive increase (Table 2).

A  $\geq 50\%$  decrease in seizure frequency was observed in 11 patients (34%) during the study, distributed as follows: 56% in the first month, 44% in the third month, and 25% in the sixth month (Table 3).

Weight loss was associated with a  $\geq 50\%$  decrease in seizure frequency (RR: 7.2; 95% CI: 1.3–39.5;  $P = .02$ ); mainly during the first month (RR: 10; 95% CI: 1.1–97;  $P = .02$ ) and the third month (RR: 8; 95% CI: 1.3–48.6;  $P = .02$ ).

Only 2 patients with frontal epilepsy remained seizure-free during the first month (one with a previous seizure frequency of 4–5 per month, and another with 40). Unifocal epilepsy also showed a more pronounced decrease in the mean number of seizures than multifocal epilepsy, especially during the first month (5 [2.9] vs 16 [3.9];  $P = .04$ ).

Antiepileptic treatment had to be readjusted due to worsening of seizure control in 3 patients with multifocal epilepsy, who stopped the diet before the third month.

Improvements  $> 50\%$  on the Huttenlocher scale were associated with: a) good to moderate adherence in the first and third months (RR: 11; 95% CI: 1.12–112;  $P = .02$ , and RR: 1.54; 95% CI: 1.08–2.19;  $P = .01$ ; respectively); b) low weight in the first and third months (RR: 0.52; 95% CI: 0.34–0.80;  $P = .02$ , and RR: 18.28; 95% CI: 1.90–175;  $P = .02$ , respectively); c) similar quantitative improvements at each visit: in the first month (RR: 102; 95% CI: 8.27–125;  $P = .001$ ); in the third month (RR: 104; 95% CI: 8.45–127;  $P = .001$ ); and in the sixth month (RR: 161; 95% CI: 8.87–292;  $P = .001$ ), and d) improvements in EEG results (Panico scale) in the first month (RR: 10.80; 95% CI: 1.16–100;  $P = .02$ ), and in the third month (RR: 2.54; 95% CI: 1.60–4.03;  $P = .03$ ) (Table 4).

To estimate the clinical relevance of seizures, we assessed the decrease in seizure frequency and obtained an absolute risk  $< 50\%$ ; a reduction  $> 50\%$  in RR, and a number needed to treat to predict seizures of 2 patients.

### Clinical and laboratory tolerance of the modified Atkins diet

Five patients (15.6%) presented adverse reactions: nausea ( $n = 5$ ), constipation ( $n = 2$ ), hyporexia ( $n = 1$ ), somnolence ( $n = 1$ ), headache ( $n = 1$ ), and hypoglycaemia-associated autonomic failure ( $n = 1$ ). The severity of these reactions was considered moderate in 2 patients (one with recurrent headache and another with intermittent hypoglycaemia, who were assessed in the emergency department but did not require hospitalisation) and mild in the remaining patients; none was considered severe. Reactions lasted less than a month in 3 patients and longer in the 2 patients with headache and hypoglycaemia.

All patients presented normal body mass index or overweight, with none presenting obesity; weight losses or gains greater than 5 kg were considered. Weight loss was observed in 9 patients (28.1%), but was not a cause of concern for the physician or patient, whereas 6 (18.8%) showed weight gain; 2 of these gained almost 10 kg, and 2 women reported body image concerns.

Patients with low to normal weight more frequently showed good to moderate adherence to the diet (RR: 24, 95% CI: 2.5–222;  $P = .006$ ).

All laboratory tests of serum samples showed parameters within normal ranges, with the exception of lipids, glucose, and transaminases. Hyperlipidaemia was detected in 10 patients (31.2%); total cholesterol level ranged from low to moderate throughout the study.

**Table 3** Degree of improvement in seizures.

Decrease in seizure frequency	$\geq 70\%$ (n)	$\geq 50\%$ (n)	$\leq 25\%$ (n)
General	12.5 (4)	34.4 (11)	43.8 (14)
1st month	21.9 (7)	56.3 (18)	18.8 (6)
3rd month	18.8 (6)	43.8 (14)	46.9 (15)
6th month	9.4 (3)	25 (8)	31.3 (10)

**Table 4** Clinical and EEG response to the modified Atkins diet, assessed with the Huttenlocher and Panico criteria.

Clinical response	1st month, n (%)	3rd month, n (%)	6th month, n (%)
1) > 50%	19 (59.4)	15 (46.9)	8 (25)
2) < 50%	13 (40.6)	17 (53.1)	24 (75)
EEG response	1st month, n (%)	3rd month, n (%)	6th month, n (%)
1) > 50%	10 (31.3)	4 (12.5)	1 (3.1)
2) < 50%	22 (68.8)	28 (87.5)	31 (96.9)

(from 190 to 230 mg/dL) in 9 (28.1%) and triglyceride level increased mildly (200–250 mg/dL) in one.

Transaminases increased to twice their normal level in a patient with mild liver disease, with no other alterations in the liver function test.

### Adherence to the modified Atkins diet

Patients reported good compliance with the diet in 19 cases (59.4%), and poor compliance in 6 (21.9%); these considerations were maintained in the scheduled follow-up visits.

Good to moderate adherence was significantly associated with a  $\geq 50\%$  decrease in seizure frequency in the first month (RR: 9.4; 95% CI: 0.9–93.6;  $P = .04$ ), and in the third month (RR: 0.4; 95% CI: 0.30–0.69;  $P = .02$ ).

After follow-up, the Morisky-Green adherence questionnaire showed diet adherence of 50%, and patients were invited to continue with the diet, as the majority had experienced no adverse reactions.

The MAD was progressively abandoned by 7 patients (21.8%); 4 before the third month and 3 after; of the latter, 2 patients reported moderate adverse effects (headache and hypoglycaemia) that influenced this decision.

### Discussion

Our study shows that MAD had a positive effect and was well tolerated in DRE, as reported in studies in adults,<sup>14,15,17,27</sup> although the results are not as uniform nor as outstanding as in the paediatric population.<sup>6,11,13,28</sup>

With regard to effectiveness, there was an acceptable decrease in the frequency of seizures in general ( $\geq 70\%$  in 12.5% of patients and  $\geq 50\%$  in 34%), with a progressive decrease at 6 months. This  $\geq 50\%$  improvement was reported in 56% of patients in the first month, in 44% at 3 months, and in 25% at 6 months. This decrease in effectiveness coincides with the results of other authors,<sup>14,17,27</sup> but not with those reported by Zare et al.,<sup>15</sup> who observed a progressive improvement from the second month.

Some researchers have suggested that the diet becomes effective after a few weeks or up to 2 months<sup>14,15,29</sup>; we support this hypothesis, as a benefit was achieved from the first month, whereas other authors report that 3 months<sup>27</sup> or longer<sup>16</sup> are needed.

We observed a greater benefit in seizure control in patients who showed better adherence to the diet and weight loss.<sup>14</sup>

Our study included patients with multifocal DRE (none with generalised epilepsy), who showed a notable decrease in seizure frequency. This result contradicts the data reported by Kverneland et al.<sup>16</sup> in a similar group, reporting a 25% seizure reduction.

The usefulness of ketosis in focal epilepsy, compared to idiopathic epilepsy, remains controversial.<sup>30–33</sup> Only 2 of our patients were seizure-free during the first month, and presented low seizure frequency subsequently.

Regarding the tolerability of the MAD, and in line with the literature,<sup>14–17,29,31</sup> we observed that it is admissible in adults, con-

sidering the low rate of clinical and laboratory adverse reactions, which lasted less than one month.

Two patients with persistent headache and hypoglycaemia were advised not to continue the diet; after discontinuing it, symptoms remitted. It should be noted that one of them already had chronic headache with exacerbations, whereas the other presented mild chronic liver disease, as well as a mild, reversible increase in transaminases.<sup>15</sup>

Weight loss associated with adequate adherence and better control of epilepsy was only reported by Kossoff et al.,<sup>14</sup> in addition to our own findings. The weight gain in 6 patients (18.8%) was attributed to the simultaneous use of MAD and the typical intake of carbohydrates, which had an influence on the decision to stop the diet, particularly in women, at a ratio of 3:1.

Three patients presented moderate loss of control of epileptic episodes, and their doses of antiepileptics had to be modified or increased. This was attributed to several factors, including lack of control of seizures with no apparent cause and, in relation to the MAD, lack of adherence, low satisfaction with the restricted carbohydrate intake, and early perception of ineffectiveness with no direct association with the diet, as they followed it for a short period of time. The increase in seizure frequency is also addressed in other studies.<sup>16,30,34</sup>

Our sample presented no metabolic comorbidities, with the exception of 2 patients who showed hypothyroidism and one patient with liver disease. Hyperlipidaemia was the most frequent laboratory finding,<sup>35</sup> occurring in 31% of the patients during the study period, with a predominance of total hypercholesterolaemia, ranging from mild to moderate severity. Chronic hyperlipidaemia predisposes to atherosclerotic cardiovascular factors<sup>36,37</sup>; therefore, prolonged use of the MAD should be assessed. The literature includes one follow-up study confirming its safety,<sup>17</sup> but further reports are needed.

The honest perception of diet compliance (59%)<sup>34</sup> was confirmed by the result of the adherence test (50%); this has not been reported by other authors. Adherence was initially good (first month), showing a positive tendency up to the third month, but subsequently decreased, particularly due to the difficulty in adapting the diet; this has been reported previously in the literature.<sup>14,17,27</sup> We observed early non-conformity, with 12.5% of the patients showing lack of adherence and refusal before the third month, and a subsequent two-fold increase (22%). This value is similar to the rate of discontinuation reported in the literature (14%–42%) in a period of one to 6 months.<sup>14,29,30</sup>

Of the 7 patients who discontinued the diet, 3 made this decision due to adverse reactions (headache, hypoglycaemia, and weight gain), 2 due to the restricted carbohydrate intake, and the other 2 due to early perception of ineffectiveness. Other reasons mentioned were apathy and a secondary behaviour disorder, which hinders flexibility in decision making.

The frequent, prolonged use of MAD and the ketogenic diet in the paediatric population, with a low rate of discontinuation,<sup>12,13,28</sup> shows that parental care is probably a determinant factor, as supervision in adults with epilepsy seems to be less strict.

Regarding limitations, our study included a small, non-randomised sample, and participants were not blinded. Furthermore, we omitted the ketones in urine test due to errors in data reporting by patients. Despite this, we should bear in mind that numerous studies confirm the lack of correlation between levels of ketones and effectiveness in controlling seizures.<sup>38,39</sup>

## Conclusion

The MAD applied to adult patients with DRE shows moderate effectiveness and adherence, and adequate tolerability. Adherence decreased over the follow-up period, with no association with adverse events; this was probably due to a preference for a diet based on carbohydrates.

## Funding

None.

## Conflicts of interest

None.

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