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FULL-LENGTH ORIGINAL RESEARCH

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Effect of modified Atkins diet in adults with drug-resistant focal epilepsy: A randomized clinical trial

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Summary

Objective: Ketogenic diets reduce seizures in children with drug-resistant epilepsy. Whether adults benefit from similar treatment has not been clarified. We therefore examined the efficacy of the modified Atkins diet in adults with drug-resistant focal epilepsy.

Methods: We performed a randomized clinical trial (RCT) with patients >16 years who had at least 3 seizures per month despite having tried at least 3 antiepileptic drugs. They were randomized to either 12 weeks on the modified Atkins diet (diet group) or habitual diet (control group). Primary endpoint was a change in seizure frequency from baseline to the intervention period, comparing those on diet with controls.

Results: We assigned 37 patients to the diet group and 38 to the control group. Nine of the patients in the diet group and 4 controls were excluded. Of those who completed the dietary intervention (n = 24), median seizure change was −1.0 (interquartile range [IQR] −13.7-8.8), while in the control group (n = 32) the median change was 4.5 (IQR −4.8-33.5). The median difference between the groups was −7.0 (95% confidence interval [CI] −37.0-3.0; P = .21). In the intention-to-treat analysis, the relative risk (RR) for achieving >50% seizure reduction was 1.8 (95% CI 0.3-10.2; P = .65), while for achieving >25% seizure reduction RR was 2.43 (95% CI 0.94-6.28; P = .06). We observed no serious adverse events.

Significance: In this RCT investigating the effect of an adjunctive modified Atkins diet on seizure frequency in adults with difficult-to-treat focal epilepsy, we found a significant reduction in seizure frequency in the diet group compared to the controls, but only for moderate benefit (>25% seizure reduction) among those who completed the intervention. However, seizure response varied considerably between individuals, perhaps negatively influenced by a drop in serum concentrations of antiepileptic drugs.

KEYWORDS
adults, focal epilepsy, ketogenic diet, modified Atkins diet, treatment

1 | INTRODUCTION

Among adults, focal epilepsies constitute 75%-80% of the epilepsies.[1] About two-thirds of these patients achieve acceptable seizure control with antiepileptic drugs (AEDs), whereas the remaining one-third is termed refractory or drug resistant. For these latter patients, other therapy options are needed, and dietary treatment may be a possibility.

The high-fat, low-carbohydrate ketogenic diets are used widely for treatment of refractory epilepsy in children. There are 2 main diet variants: (1) the classical ketogenic diet with precalculated meals and a ketogenic ratio (fat to protein plus carbohydrate) of 2.5-4.0, and (2) the less-demanding modified Atkins diet where carbohydrate is limited to 15-20 g/d and high fat intake is encouraged. A review from 2016 concluded that such diets have a pronounced seizure-reducing effect in children,[2] but solid evidence of a seizure-reducing effect of these ketogenic diets among adults is lacking. Klein et al reviewed dietary treatment of 132 adult patients included in 10 nonrandomized studies (the number of participants ranging from 7 to 30).[3] They found that 32% of those using ketogenic diet and 29% of those using modified Atkins diet achieved >50% seizure reduction. Of these, 9% and 5%, respectively, achieved >90% seizure reduction. The proportions of patients with generalized vs focal epilepsy were not specified in all the studies, thus comparing the efficacy between the 2 epilepsy types was not meaningful.

Adherence to these diets is a challenge. Klein et al called attention to a high degree of discontinuation, and Ye et al suggested that adults may be more compliant with the modified Atkins diet than with the classical ketogenic diet.[3,4]

The aim of this randomized clinical trial (RCT) was thus to assess the effect on seizure frequency of adding a modified Atkins diet to current drug treatment in adults with drug-resistant focal epilepsy.

Key Points

- This trial examined the effect of modified Atkins diet on seizure frequency in adults with drug-resistant focal epilepsy
- It was a randomized clinical trial; the dietary treatment lasted for 12 weeks
- With cutoff of 25% but not with 50%, there was a significant reduction in seizure frequency
- There was considerable individual variation in seizure response, and the diet was beneficial to some patients demonstrating the need for further studies

2 | METHODS

2.1 | Study design

This was a 2-armed, open RCT with one diet group and one control group. The study was performed at the National Center for Epilepsy, a tertiary referral center in Norway. It was approved by the Regional Committee for Medical and Health Research Ethics in South-East of Norway (number 2010/2326).

2.2 | Participants

Between March 1, 2011, and February 28, 2017, a total of 277 patients were contacted and screened. The participants were recruited from all over Norway. As part of the screening for eligibility, potential candidates received oral and written information about the study. Written consent was signed by all participants.

Eligible patients should be >16 years; have focal or multifocal epilepsy according to the International League Against Epilepsy's classification[5]; have at least 3 countable seizures per month, having tried at least 3 AEDs, including current treatment; a body mass index >18.5 kg/m^2; and they should be motivated for and capable of adhering to the diet, and if required, with assistance. Exclusion criteria were pregnancy, use of ketogenic diets in the previous 12 months, change in antiepileptic treatment, psychogenic nonepileptic seizures, status epilepticus the previous 6 months, having undergone resective surgery or vagus nerve stimulator implantation during the previous 12 months, or comorbidities that contraindicated using the diet.

2.3 | Randomization

Participants were randomized (1:1) to either 12 weeks of treatment with the modified Atkins diet (diet group) or their habitual diet (control group). Before inclusion, randomization was performed by an independent scientist not involved in the study and not taking part in follow-up or evaluation of the patients. The patients were consecutively randomized. A staff member not involved in the study generated the random allocation sequence manually, and the study group allocation was forwarded to the first author for each enrolled patient.

Inclusion was performed by a senior consultant (KON or EM) and a clinical nutritionist (MK).

2.4 | Procedures

The trial consisted of a baseline period lasting 12 weeks followed by a 12-week intervention period where patients

in the diet group consumed the modified Atkins diet, whereas the control group consumed their habitual diet (ie, the same diet as they ate during the baseline period).

Participants in both groups were admitted to a short hospital stay, if necessary with caregivers, for data collection before starting the intervention period. During the admission, diet instruction was given to participants in the diet group. Alternatively, the diet instruction was given in the residential home of the patient, in order to inform a group of personnel responsible for the day-to-day diet preparation, seizure registration, and follow-up.

The effects of the diet were evaluated during 1-day hospital admissions in weeks 4 and 12 after diet initiation. To evaluate diet adherence, ketosis was assessed daily with urine dipsticks (Ketostix, Bayer Healthcare, Leverkusen, Germany), using the first urine morning sample and a sample collected before the last meal of the day. Mean urine ketosis during the 12 weeks on the diet was then calculated. Adverse effects were assessed 4 and 12 weeks after start of the intervention period using a semi-structured questionnaire. During the intervention period, the controls were contacted per telephone twice and they delivered a 3 days' dietary record obtained between weeks 4 and 6. Those allocated to the control group were offered dietary treatment after completion of the study.

To rule out nonsymptomatic kidney stones, a renal examination was performed by either ultrasound or computer tomography prior to study start. Prophylactic oral potassium citrate (Cytra-K Crystals, Cypress Pharmaceutical Inc., Madison, MS, USA) was given to those with current or previous kidney stones or with kidney stones in the family.

Seizure frequency was recorded both during the 12-week baseline period and during the 12-week intervention period. Seizure types were classified by an experienced neurologist prior to inclusion and were based on seizure semiology and (electroencephalography (EEG) findings. To disclose structural abnormalities, cerebral magnetic resonance imaging (MRI) was performed in all patients. The seizures had to be countable either by the patient or the caregivers. All seizures were recorded in paper diaries and reviewed by the study team at each visit.

The current treatment with AEDs and/or vagus nerve stimulation was kept unchanged in both study groups throughout the study period. If an AED was added or removed, baseline seizure registration would be delayed by 3 months, whereas if adjusting an AED dose, the delay would be 4 weeks.

Venous blood was collected after an overnight food and drug fast. We assessed serum levels of current AEDs and various biomarkers in blood. All biochemical analyses were performed by standard methods at Oslo University Hospital.

The diet was started at home on a preplanned date. In agreement with the diet described by Kossoff et al, a maximum of 16 g carbohydrate per day was allowed.[6] In the Norwegian Food Composition Table, the amount of carbohydrate specified in foods exclude fibers. Thus, carbohydrate that was limited to 16 g in the intervention diet were those digestible by the small intestine, while fibers were eaten in free amounts. We encouraged high-fat foods but did not limit protein or total energy consumption. Medical nutrition products were not encouraged but used as supplements when appropriate. The participants received a booklet with recipes of breads, crackers, cakes, vegetable dishes, and other suitable dishes. The breads, crackers, and cakes are made by very-low-in-sugar/high-in-fiber ingredients such as seeds (flax seeds, sesame seeds), bran, psyllium husks, eggs, nuts, cream, cottage cheese, margarine and plant oils. Patients also received suggestions for a daily menu. For some patients living in residential homes, an energy-adjusted menu was prepared. One participant was fed by gastrostomy. A daily fluid intake of 2-3 L was recommended to reduce the risk of kidney stones. One multivitamin tablet ("Multi," Nycoplus, Takeda, Asker, Norway) and 800 mg calcium from pure calcium carbonate (Takeda) were provided as daily supplements. The supplements were free of carbohydrates.

2.5 | Outcomes

Primary endpoint was a change in seizure frequency from baseline to the intervention period, comparing participants on the diet with controls. Secondary outcomes were proportion of patients with >50% and >25% seizure reduction, adverse effects, change in body weight, changes in selected biomarkers of metabolism (aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], free carnitine, total carnitine, uric acid, hemoglobin A1c (HbA1c), total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides), serum concentrations of AEDs, and change in seizure severity using the revised Liverpool Seizure Severity Scale (LSSS) (scale: 1-100 points, score reduction indicates reduced severity).[7] The LSSS questionnaire was not facilitated for intellectually disabled participants. Percent average change in serum concentration of AEDs was calculated by taking the average percent change of all AEDs measured.

2.6 | Statistical analysis

For sample size calculation, a reduction in seizure frequency of 25% was defined as the minimum outcome of clinical importance, as proposed by Neal and colleagues.[8] With a power of 80% and a significance level of 5%, 35 participants were required in each group to detect a 25%

difference in mean percentage of baseline seizures between the groups (standard deviation in each group as in Neal et al[3]: 37%). Adding 30% dropout, a total of 92 participants were to be included.

Data are presented as mean (95% confidence interval [CI]), median (interquartile range [IQR] or 95% CI), or frequency (%), as appropriate. We tested for differences in baseline characteristics by Mann-Whitney *U* test for continuous variables and by Fisher's exact or chi-square tests for categorical variables. For the primary outcome, we compared seizure frequency during 12 weeks of intervention in the 2 groups, adjusting for baseline seizures by analysis of covariance (ANCOVA) as recommended by Vickers and Altman.[9] Due to skewness, the baseline and intervention seizure frequencies were $\log_e$-transformed. Hodges-Lehman's method was used to estimate the difference in medians between the 2 groups with 95% CI. For the secondary outcomes, group differences after the 12-week intervention period were also tested using ANCOVA adjusting for baseline values. If skewed, $\log_e$-transformation was used and group differences estimated by Hodges-Lehman's method. The proportions of patients who achieved >50% and >25% seizure reduction in the diet vs control group were calculated as mean weekly seizure frequency from baseline to weeks 5-12 in the intervention period, with 95% CI. Fisher's exact and chi-square tests were used to test differences between the 2 groups in >50% and >25% seizure reduction, respectively. In the diet group, ANCOVA was used to compare patient who lived in residential homes and patients who administered themselves as regarding urine ketosis and seizure frequency during 12 weeks of intervention (the latter was $\log_e$-transformed). These results must be interpreted with caution due to the low numbers. In the diet group, we also calculated Spearman correlation coefficient, *r*, to estimate the association between percent change in serum concentration of AEDs and percent change in seizure frequency after 12 weeks of dietary treatment. Participants who started the intervention were included in the intention-to-treat analysis. IBM SPSS statistics version 25 (IBM, Armonk, NY, USA) was used for the statistical analyses. The trial was registered with ClinicalTrials.gov (ID NCT01311440).

3 | RESULTS

Due to slow recruitment, we chose to stop inclusion after 6 years with 75 participants who met the inclusion criteria and elected to participate (Figure 1). They were randomized to either the diet (n = 37) or control (n = 38) group. Twenty-eight of the 37 in the diet group started the diet. In the control group, 3 were lost before start, and one was later excluded because he commenced the dietary treatment, thus leaving 62 patients: 28 in the diet group and 34 in the control group for intention-to-treat analysis. Moreover, 24 diet patients and 32 controls completed the 12-week intervention period and were available for on-treatment analysis and evaluation of secondary outcomes. The reasons for not starting the diet, for early discontinuation of the diet, and for exclusion from the control group are given in Figure 1.

Baseline demographic and clinical characteristics of the study sample are presented in Table 1. Patients in the 2 study groups were comparable in demographic, and disease- and treatment-related characteristics. The ethnicity was Caucasian except one African and one Sami in the control group.

No difference ($P = .21$) was found between the groups in seizure frequency after the intervention (Table 2). After the 12-week intervention period, none of the participants in the 2 study groups were seizure-free. Two participants in the diet group experienced a near tripling of seizures, whereas 2 participants in the control group had a reduction in the number of seizures by more than 70% (Figure 2). In the intention-to-treat analysis, 3 patients in the diet group experienced >50% seizure reduction compared to 2 in the control group (relative risk [RR] 1.8, 95% CI 0.3-10.2; $P = .65$). The corresponding RR for achieving >25% seizure reduction was 2.43 (95% CI 0.94-6.28; $P = .06$). Among the 24 in the diet group and 28 in the control group who completed the intervention (on-treatment), the RR for achieving >25% seizure reduction in the diet group vs the control group was 2.67 (95% CI 1.05-6.79; $P = .03$).

The mean morning and evening levels of urine ketosis among the patients in the diet group during the 12-week intervention period were 2.9 mmol/L (95% CI 1.6-4.1) and 5.9 mmol/L (95% CI 2.2-8.0), respectively (n = 21; 3 with missing data), indicating satisfactory adherence to the diet. Of the 24 patients in the diet group, 6 lived in residential homes, while 18 administered the diet themselves. We found no significant difference in seizure frequency or urine ketosis between whose living in residential homes and the others ($P = .66$ and $P = .35$, respectively).

There were no serious adverse events, but 3 of the 28 patients who received the diet for at least 1 week, terminated the diet early due to increased seizure frequency. Although gastrointestinal symptoms were mostly mild and transient, nausea and vomiting was the reason for early termination in one patient. Furthermore, 6 patients (25%) in the diet group reported nausea, vomiting, or reflux; 4 (17%) reported constipation, and 2 (8%) had diarrhea. Three patients (13%) experienced a transient seizure increase during the first 2-3 weeks on the diet but had good seizure-reducing effect later. Other patient-reported adverse effects were reduced energy reported by 8 patients (33%), social stigma due to the diet by 5 (21%), and reduced exercise

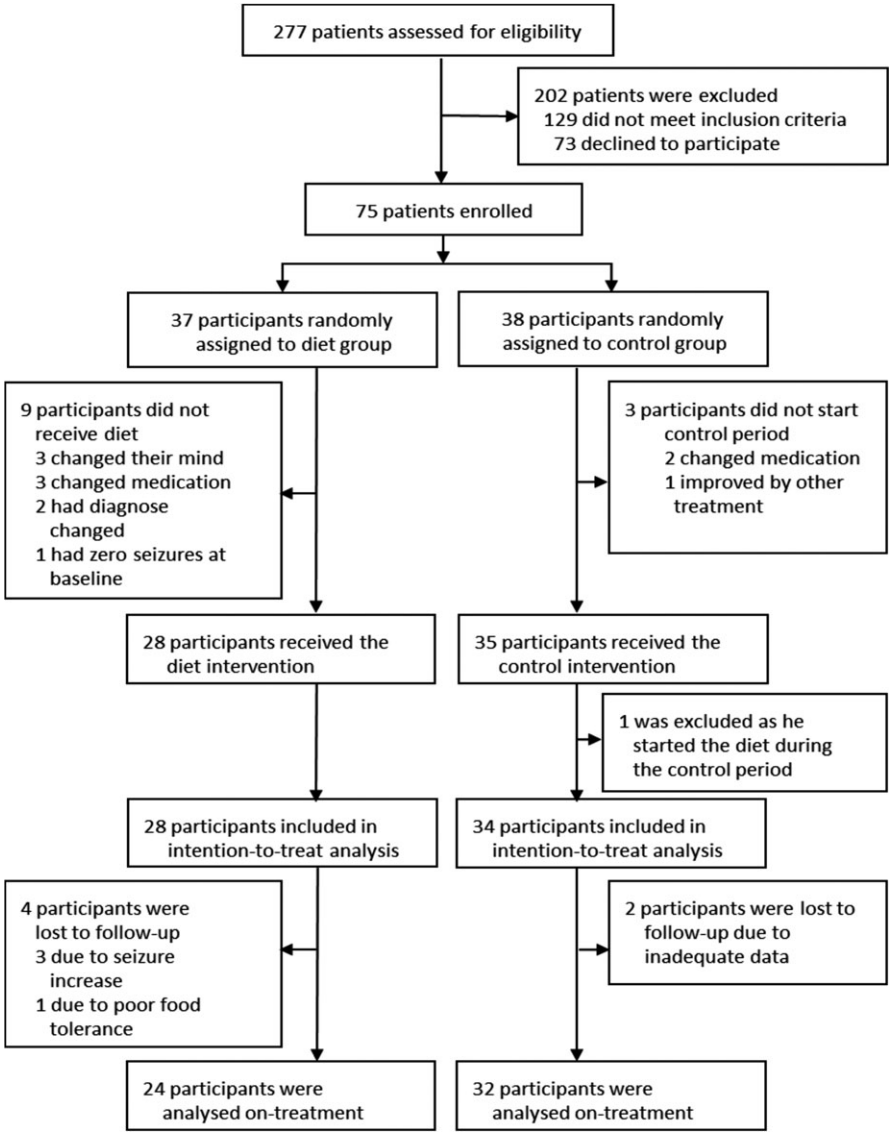

FIGURE 1 Trial profile

capacity by 4 (17%). Three patients (13%) experienced reduced appetite as a problem, 2 (8%) had anxiety, and 2 (8%) had abdominal pain. Undesirable weight reduction, reduced sleep quality, and skin rash were also reported, each symptom by one patient. Of the 9 women who had menstruation, one (4%) experienced longer and irregular periods and increased discharge. No symptoms of kidney stones were reported during the intervention period.

Mean baseline body weight was 78 kg (95% CI 69-87) in the diet group vs 77 kg (95% CI 71-82) in the control group. After the 12-week intervention period, the mean intergroup difference was −4 kg (95% CI −6-2; $P < .001$), weight was unchanged in the control group. Weight loss was wanted among those overweight, while for a few the weight loss was undeliberate.

Results from the blood biochemistry measurements are summarized in Table 3. After the 12-week intervention, the concentrations of free and total carnitine were significantly reduced in the diet group compared to the controls ($P < .001$ and $P = .04$, respectively). In 5 diet patients, free carnitine decreased below the reference interval of 19-50 lmol/L, and 4 of them had total carnitine under the reference interval of 20-58 lmol/L. Moreover, all of these 5 patients reported reduced energy, which may be a symptom of carnitine deficiency.

One diet patient with a prominent fall in carnitine also reported shortness of breath, dizziness, and palpitations during the first weeks on the diet. Three patients in the diet group with low carnitine reported muscular weakness and reduced exercise capacity. Uric acid increased considerably in some patients, but the values normalized after dietary advice about minimalizing food that may increase uric acid (such as anchovy, sardines, mackerel, herring, entrails, and bouillon), and favoring intake of green vegetables. There was a significant negative difference in HbA1c values for the diet vs control after 12 weeks of intervention ($P = .001$). In the control group, mean (95% CI) HbA1c was 5.3% (5.2-5.4%) at baseline and 5.2% (5.1-5.3%) after

TABLE 1 Baseline characteristics of the 2 study groups[a,b]

	Diet group (n = 28)	Control group (n = 34)
Age (y)	36 (32-40)	37 (32-41)
Sex		
Female	19 (68%)	16 (47%)
Male	9 (32%)	18 (53%)
Epilepsy etiology		
Structural	5 (18%)	11 (32%)
Infectious	2 (7%)	4 (12%)
Unknown	21 (75%)	19 (56%)
Age at first seizure (y)	14 (8-19)	11 (7-14)
Years with epilepsy	22 (17-27)	25 (21-30)
Intellectually disabled	9 (32%)	13 (38%)
Employment		
Paid employment	9 (32%)	4 (12%)
Disabled	17 (61%)	26 (80%)
Other	2 (7%)	3 (9%)
Need help to calculate or prepare food	14 (50%)	17 (50%)
Vagus nerve stimulator (previous or current)	14 (50%)	16 (47%)
Epilepsy surgery	7 (25%)	7 (21%)
Number of AED tried	9 (7-10)	10 (8-11)
Number of current AEDs	2.2 (1.8-2.6)	2.1 (1.8-2.4)

AED, antiepileptic drug.
[a]Data are mean (95% confidence interval) or frequency (%).
[b]No baseline characteristics were different between the 2 groups.

the intervention, while it was reduced from 5.3% (5.0-5.5%) to 5.0% (4.8-5.2%) in the diet group. Furthermore, there was a significant increase in total and LDL cholesterol in the diet group (P = .01 and P = .001, respectively) (Table 3). HDL cholesterol and triglycerides were unchanged.

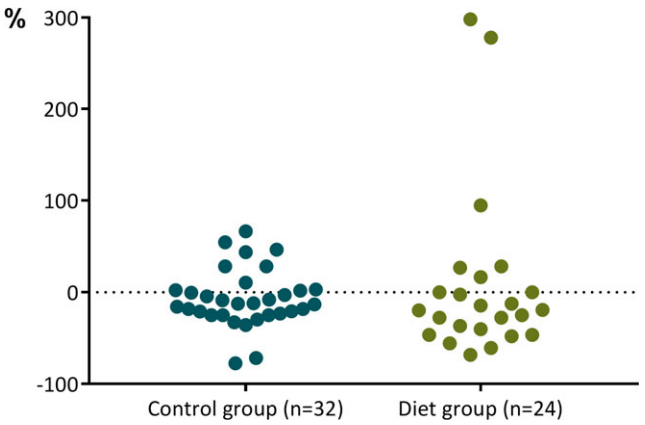

FIGURE 2 Percent change in seizure frequency from baseline to intervention period

Mean percent serum concentrations of AEDs dropped by 16% (95% CI −8-23) in the diet group compared to the controls (P < .001). In the diet group, we found no significant correlation between percent change in serum concentration of AEDs and percent change in seizure frequency after 12 weeks of dietary treatment as illustrated in Figure 3, in the whole diet group (r = .24, P = .24, n = 24) or after exclusion of the 3 outliers who experienced >100% seizure exacerbation (r = .29, P = .20, n = 21). Table 4 shows the change in serum concentration of the different AEDs.

Mean baseline LSSS score was 44 points (95% CI 34-53) in the diet group (n = 19) and 46 points (95% CI 37-55) in the control group (n = 19). At the end of the intervention period, the mean difference between the 2 study groups was −7 points (95% CI −16-1; P = .10).

4 | DISCUSSION

In this RCT we investigated the effect of adjunctive modified Atkins diet on seizure frequency in adults with difficult-to-treat focal epilepsy. We found a significant seizure

TABLE 2 Intergroup comparison of seizure frequency; change from baseline to intervention period

Seizures	Diet group n = 24 Median (IQR[c])	Control group n = 32 Median (IQR[c])	Intergroup comparison Median (95% CI)[d]	P-value[e]
Baseline[a]	39.5 (19.5-121.0)	46.5 (22.5-171.5)	–	–
Intervention[a]	32.0 (18.5-112.3)	48.0 (19.8-155.5)	–	–
Difference[b]	−1.0 (−13.7-8.8)	4.5 (−4.8-33.5)	−7.0 (−37.0-3.0)	.21

[a]Sum of seizures during 12-week baseline and intervention periods.
[b]Difference = baseline − intervention.
[c]Due to skewed data we present median with interquartile range (IQR).
[d]Hodges-Lehman estimate of difference in the medians of the 2 groups (diet vs control) with 95% confidence interval (CI).
[e]Adjusting for baseline by analysis of covariance as recommended by Vickers and Altman.[9] Due to skewness, data were $\log_e$-transformed.

TABLE 3 Blood biochemistry in the two study groups at baseline and comparison of the groups after the 12-week intervention period

	Diet group (n = 21-24)[a] Baseline Mean (95% CI)	Control group (n = 29-32)[a] Baseline Mean (95% CI)	Inter-group comparison after 12 wk intervention	
			Difference[b] (Mean 95% CI)	P-value
ASAT, mmol/L	19.1 (16.1-22.3)	20.1 (17.9-22.3)	1.5 (−2.6-5.7)	.47
ALAT, mmol/L	29.2 (21.7-36.7)	25.9 (21.1-30.7)	2.5 (−3.8-8.8)	.43
Carnitine free, mmol/L	37.8 (32.5-43.0)	31.4 (27.5-35.2)	−8.9 (−13.4-4.4)	<.001
Carnitine total, mmol/L	48.8 (43.3-54.3)	41.8 (37.1-46.5)	−5.4 (−10.5-0.3)	.04
Uric acid, ʅmol/L[c]	249 (210-289)	243 (218-268)	20 (−2-42)	.08
HbA1c, %	5.3 (5.0-5.5)	5.3 (5.2-5.4)	−0.2 (−0.4-0.1)	.009
Total cholesterol, mmol/L	5.2 (4.7-5.7)	5.3 (4.9-5.7)	0.6 (0.1-1.1)	.01
LDL cholesterol, mmol/L	3.1 (2.6-3.5)	3.2 (2.8-3.6)	0.8 (0.3-1.2)	.001
HDL cholesterol, mmol/L	1.7 (1.5-2.0)	1.6 (1.5-1.8)	−0.0 (−0.1-0.1)	.95
Triglycerides, mmol/L[d]	0.8 (0.6-1.2)	0.9 (0.6-1.5)	0.0 (−0.1-0.2)[d]	.75

[a]The variation in n is due to missing data.
[b]Difference between the groups at the end of the 12-week intervention period (diet vs control), adjusted for baseline values by analysis of covariance.
[c]Reference 230-480 ʅmol/L.
[d]Due to skewed data we present the medians with interquartile range at baseline. Triglyceride data was transformed with natural logarithm in the analysis of covariance.
[e]Hodges-Lehman estimate of difference in the medians of the two groups (diet vs control) with 95% CI.[25]

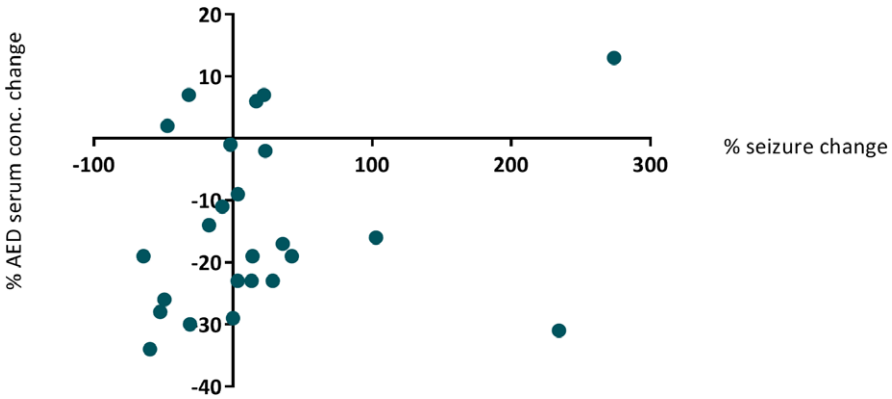

FIGURE 3 Percent change in seizure frequency vs percent change in serum concentrations of antiepileptic drugs (AEDs) from baseline to intervention period; diet group only. No correlation was found

reduction in the diet group compared to controls, but only for moderate benefit (25%-50% seizure reduction).

Recently, an Iranian RCT using modified Atkins diet in adults reported 35.3% responders (>50% seizure reduction) vs no responders in the control group.[10] None became seizure-free after 2 months on the modified Atkins diet. In the diet group, 12 of 34 participants (35%) dropped out. The participants were classified with focal and generalized seizures, but response to the diet with respect to epilepsy type was not stated. However, this study did not comply with the CONsolidated Standards Of Reporting Trials recommendations for RCTs.

Unlike previous reports, in our study, we could not detect a reduction in seizure frequency.[3,4,10] There may be several reasons for this: (1) By using the RCT method, our study controls for seizure fluctuation due to factors other than the dietary treatment, which will not be accounted for in an uncontrolled study. (2) Our study sample constituted a particularly drug-resistant group; they had lived with epilepsy for more than 20 years on average and had a median of 15 seizures per month after having tried on average 9-10 different AEDs. We cannot rule out that their response to the treatment was poorer than in a group of patients with a shorter seizure history. (3) Although both Klein et al and Kossoff et al suggested that efficacy will be seen after a few weeks or up to 2 months on the diet,[3,6] 12 weeks on the diet may still be too short to detect a reduction in seizure frequency; in our sample, 3 of those who eventually responded experienced an initial transient seizure increase, whereas the reduction in seizure frequency and severity was seen after 2-3 months. Thus, the improvement of those 3 patients would have been detected in a study with a

TABLE 4 Changes in AED serum concentrations from before to after 12-week intervention with modified Atkins diet, comparing control (n = 32) and diet (n = 24) group

	Diet group		Control group		Intergroup comparison	
	Before intervention Mean (95% CI) lmol/L	Percent change Mean (95% CI) %	Before intervention Mean (95% CI) lmol/L	Percent change Mean (95% CI) %	Difference Mean (95% CI) lmol/L	P-value
CBZ	n = 4 35.6 (28.9-42.4)	n = 4 −31.0 (−49.6-12.5)	n = 7 35.4 (28.6-42.2)	n = 7 7.6 (−15.6-30.7)	−13.2 (−22.9-3.5)	.014
ZNS	n = 2 71.5 (56.3-86.7)	n = 2 −35.4 (−111.4-40.5)	n = 3 90.4 (−26.0-206.7)	n = 3 −10.3 (−77.0-56.4)	−16.7 (−90.2-56.8)	.43
LEV	n = 5 71.8 (34.7-108.9)	n = 5 10.5 (0.1-20.9)	n = 8 100.8 (51.3-150.2)	n = 8 −0.3 (−15.8-15.2)	8.3 (−6.2-22.7)	.23
VPA	n = 6 495.7 (424.4-567.0)	n = 6 −18.4 (−36.6-0.2)	n = 10 453.0 (303.8-602.2)	n = 10 −4.2 (−14.7-6.2)	−61.4 (−131.0-8.2)	.08
TPM	n = 5 27.5 (20.5-34.5)	n = 5 −12.0 (−38.0-13.9)	n = 3 24.2 (2.2-46.2)	n = 3 7.6 (−44.6-59.7)	−3.6 (−11.9-4.8)	.32
OXC	n = 8 85.8 (71.6-99.9)	n = 8 −6.1 (−20.6-8.5)	n = 10 83.4 (60.5-106.3)	n = 10 3.5 (−6.6-13.7)	−7.2 (−21.5-7.2)	.30
CLB[a]	n = 3 5.9 (−3.0-14.8)	n = 3 −26.1 (−43.4-8.8)	n = 5 3.9 (0.9-6.8)	n = 5 −0.6 (−13.5-12.4)	−1.3 (−2.5-0.1)	.035
LTG	n = 8 26.9 (16.5-37.2)	n = 8 −9.7 (−21.9-2.4)	n = 5 38.3 (25.1-51.5)	n = 5 2.6 (−6.9-12.1)	−4.7 (−10.6-1.1)	.10
LCM	n = 3 16.3 (2.7-30.0)	n = 3 −19.5 (−47.2-8.2)	n = 1 19.0	n = 1 31.6	–	–
PGB	n = 0	–	n = 2 15 (2.3-27.7)	n = 2 20.5 (−81.6-122.6)	–	–
CZP	n = 1 25	n = 1 −36	n = 1 72	n = 1 −4.2	–	–
PB	n = 0	–	n = 2 30.5 (−141.0-202.0)	n = 2 −2.5 (−120.5-115.6)	–	–
PHT	n = 1 40	n = 1 −12.5	n = 2 52 (13.9-90.1)	n = 2 −6.3 (−111.6-99.1)	–	–

AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; TPM, topiramate; VPA, valproate; ZNS, zonisamide.
[a]Desmethylclobazam.

longer lasting intervention period. (4) Classical ketogenic diet is said to represent a "higher dose" of the treatment than the modified Atkins diet, explained by a higher ratio between fat and carbohydrate plus protein. As in children, some adults may respond better to the classical ketogenic diet with ketogenic ratio of 2.5-4 than to the modified Atkins diet.[11] (5) This is the first study of dietary treatment in adults with solely focal epilepsy. It has been suggested that the diets may be more effective in patients with generalized rather than in focal epilepsy, both in children and adults,[8,12–15] but the documentation is contradictory.[3] (6) Finally, the relatively low number of participants may be the reason that we were not able to find a significant seizure reducing effect of the diet.

A few extreme changes of seizure frequency were reported both in diet and control group and need to be elaborated. Two patients in the diet group experienced 274% and 234% seizure increase, respectively. One of them had a considerable drop in serum concentrations of the AEDs (zonisamide dropped 41% and carbamazepine dropped 21%), which may have been responsible for the seizure exacerbation. The seizure aggravation in the second patient is harder to explain. The patient had no fall in serum concentrations of the AEDs (in fact, the values of oxcarbazepine and levetiracetam increased by 21% and 4%, respectively). In the intervention period the patient reported to be very stressed, partly due to an exam, partly due to the challenging diet. Moreover, a diet-induced increase in seizure frequency has been reported by others.[3,4] There were no obvious explanations for the considerable reduction in seizure frequency in 2 patients in the control group. In one it may have been due to seasonal variations in

seizure susceptibility, and in the other due to a particularly stressful period in baseline followed by a quieter intervention period. These variations emphasize the importance of performing randomized studies with a control group.

The LSSS score mainly reflects changes in the most disabling seizures like focal-onset tonic–clonic seizures and focal seizures with impaired awareness. Fewer or disappearance of such seizures implies a considerable reduction of LSSS score. Furthermore, a change in the postictal phase is reflected in the score. For example, in the current study a patient who normally would stay in bed the entire day after a morning seizure with confusion, headache, and sleepiness, with dietary treatment, the patient was able to carry out normal activity minutes after the seizure had terminated. A score reduction of 10 or greater is considered to be of clinical relevance.[16] After 12 weeks on the diet, 8 participants had an LSSS score reduction >10 points (range 10-55 points) compared to 2 in the control group.

We employed a pragmatic study design in order to evaluate the effectiveness of the diet in a real life setting. The enrollment (75/277; 27%) was higher than in other studies, as reviewed by Klein et al.[3] Notably, only 14% in the diet group did not complete the study period. This is a low number of dropouts compared to previous studies and may partly be explained by the shorter trial period.[3] Close follow-up and support, including thorough information, training, and abundant recipes may also have reduced the number of dropouts in the diet group.

All the patients were treated in an epilepsy center with national responsibility of dietary treatment. Because the majority of those referred to the center have difficult-to-treat epilepsies, our results cannot be generalized to an ordinary epilepsy population.

Kidney stones are a relatively common diet-induced problem among children on ketogenic diets.[17,18] However, none of our patients experienced kidney stones, possibly due to adequate liquid consumption combined with potassium-citrate in one individual who was diagnosed with a kidney stone prior to diet start. Reduced energy and/or exercise capacity was reported by 10 patients (36%) in the diet group. Of those who reported reduced energy, 5 had reduced levels of carnitine. The study did not last long enough to ascertain whether this change was transient, but our clinical experience indicates that carnitine levels and exercise capacity normalize after some months. Mean total and LDL cholesterol concentration increased moderately. Whether such change may increase the risk of cardiovascular disease is not clarified.[19]

As elaborated above, for some participants in the diet group, the seizure frequency increased substantially. An aggravated seizure frequency induced by the diet has also been reported by others.[20,21] As we have reported earlier,[22] and in line with recent findings in children,[23] we found a reduction of serum concentrations of AEDs in the diet group. Thus, a reduction in serum concentrations of AEDs could, at least partly, explain the observed seizure exacerbation. However, there was no correlation between percent change in serum concentration of AEDs and percent change in seizure frequency after 12 weeks of dietary treatment (diet group only). Regarding possible interactions between specific drugs and the diet, our limited dataset precludes firm conclusions. Nevertheless, one might speculate about the reduced serum concentrations of carbamazepine, valproate, and clobazam may be of clinical importance (Table 4).

Regarding potential comparator bias, in this study we compared a complex dietary intervention to no change in diet in the control group. Ideally, blinding should have been employed, but this would have been difficult to accomplish and was therefore ruled out. Furthermore, there were considerable differences between the 2 groups related to the intervention; time-consuming cooking, shopping for costly food, eating unfamiliar food with lots of fat in the diet group, compared to no extra cost or work in the control group. Such stressful changes experienced by those in the diet group may, in some patients with epilepsy, lead to increased seizure frequency. On the other hand, greater attention to and care for those in the diet group from the hospital staff and from people close to the patients at home could lower the seizure frequency in the diet group compared to the control group (the Hawthorne effect). To counteract such differences, we phoned the patients in the control group twice and asked for a 3-day dietary record during the 12-week intervention period. Furthermore, being included in a dietary trial may lead to a more thorough seizure recording among the diet group than among the controls, which would increase the recorded seizure frequency. Therefore, whether a potential comparator bias would increase or reduce the observed result is not clear.

To select patients who are likely to succeed with the treatment, an initial dialog between the treatment team and the patient, his/her next-of-kin and/or caregivers, discussing circumstances such as cooking skills and resources, economy, motivation, allergies, other individual limitations or strengths, and so on, is strongly recommended. Those with poor fat digestion and those who dislike cooking may be less likely to succeed. Nevertheless, we believe that patients with a disabling seizure situation who are highly motivated should be given the opportunity to attempt dietary treatment. At present it is not possible to predict who will benefit from this treatment.[24]

In conclusion, in this RCT on the effect of an adjunctive modified Atkins diet in adults with drug-resistant focal epilepsy, we found no significant seizure-reducing effect. However, because the individual variation in seizure response was considerable, and the diet was beneficial to some patients, there is a need for studies of the effect of

the diet in different subgroups, such as in different seizure types or epilepsy syndromes. A larger sample with longer follow-up is required to draw conclusions regarding the true efficacy of such treatment in adults with refractory epilepsy.

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DISCLOSURE OF CONFLICT OF INTEREST

MK received a payment from Nutricia for a lecture held in 2015. EM, POI, MBV, ET, KKS, and KON declare no conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Brodie MJ, Barry SJ, Bamagous GA, et al. Patterns of treatment response in newly diagnosed epilepsy. Neurology. 2012;78:1548–54.
2. Martin K, Jackson CF, Levy RG, et al. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev. 2016;2:CD001903.
3. Klein P, Tyrlikova I, Mathews GC. Dietary treatment in adults with refractory epilepsy: a review. Neurology. 2014;83:1978–85.
4. Ye F, Li XJ, Jiang WL, et al. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. J Clin Neurol. 2015;11:26–31.
5. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512–21.
6. Kossoff EH, Rowley H, Sinha SR, et al. A prospective study of the modified Atkins diet for intractable epilepsy in adults. Epilepsia. 2008;49:316–9.
7. Scott-Lennox J, Bryant-Comstock R, Lennox GA, et al. Reliability, validity and responsiveness of a revised scoring system for the Liverpool Seizure Severity Scale. Epilepsy Res. 2001;44:11.
8. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7:500–6.
9. Vickers AJ, Altman DG. Statistics notes: analysing controlled trials with baseline and follow up measurements. BMJ. 2001;323:1123–4.
10. Zare M, Okhovat AA, Esmaillzadeh A, et al. Modified Atkins diet in adult with refractory epilepsy: a controlled randomized clinical trial. Iran J Neurol. 2017;16:72–7.
11. Kossoff EH, Bosarge JL, Miranda MJ, et al. Will seizure control improve by switching from the modified Atkins diet to the traditional ketogenic diet? Epilepsia. 2010;51:2496–9.
12. Maydell BV, Wyllie E, Akhtar N, et al. Efficacy of the ketogenic diet in focal versus generalized seizures. Pediatr Neurol. 2001;25:208–12.
13. Groomes LB, Pyzik PL, Turner Z, et al. Do patients with absence epilepsy respond to ketogenic diets? J Child Neurol. 2011;26:160–5.
14. Kossoff EH, Henry BJ, Cervenka MC. Efficacy of dietary therapy for juvenile myoclonic epilepsy. Epilepsy Behav. 2013;26:162–4.
15. Kverneland M, Selmer KK, Nakken KO, et al. A prospective study of the modified Atkins diet for adults with idiopathic generalized epilepsy. Epilepsy Behav. 2015;53:197–201.
16. Bryant-Comstock L, Scott-Lennox J, Lennox R. Assessment of Seizure Severity with Adjunctive Lamotrigine Therapy: Results from a U.S. Observational Study. Epilepsy Behav. 2001;2:152–7.
17. Furth SL, Casey JC, Pyzik PL, et al. Risk factors for urolithiasis in children on the ketogenic diet. Pediatr Nephrol. 2000;15:125–8.
18. Kossoff EH, Pyzik PL, Furth SL, et al. Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. Epilepsia. 2002;43:1168–71.
19. McDonald TJW, Ratchford EV, Henry-Barron BJ, et al. Impact of the modified Atkins diet on cardiovascular health in adults with epilepsy. Epilepsy Behav. 2017;79:82–6.
20. Barborka CJ. Epilepsy in adults: results of treatment by ketogenic diet in one hundred cases. Arch Neurol Psychiatry. 1930;23:904–14.
21. Cervenka MC, Terao NN, Bosarge JL, et al. E-mail management of the modified Atkins diet for adults with epilepsy is feasible and effective. Epilepsia. 2012;53:728–32.
22. Kverneland M, Tauboll E, Selmer KK, et al. Modified Atkins diet may reduce serum concentrations of antiepileptic drugs. Acta Neurol Scand. 2015;131:187–90.
23. Heo G, Kim SH, Chang MJ. Effect of ketogenic diet and other dietary therapies on anti-epileptic drug concentrations in patients with epilepsy. J Clin Pharm Ther. 2017;42:758–64.
24. Schoeler NE, Cross JH. Ketogenic dietary therapies in adults with epilepsy: a practical guide. Pract Neurol. 2016;16:208–14.
25. IBM. SPSS Statistics Reference Manual. Independent Samples Tests (nonparametric tests algorithms). Hodges-Lehmann Estimates. Armonk: IBM, 1989, 2014.

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