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FULL-LENGTH ORIGINAL RESEARCH

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# Pharmacokinetic interaction between modified Atkins diet and antiepileptic drugs in adults with drug-resistant epilepsy

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## Abstract

**Objective:** The aim was to examine the influence of modified Atkins diet on serum concentration of antiepileptic drugs (AEDs).

**Methods:** Prospective data from 63 adult patients with either focal or generalized drug-resistant epilepsy recruited to 12-week dietary treatment as add-on to AEDs are analyzed. AED serum concentrations, ketones, glucose, and hemoglobin A1c were measured before and after the dietary intervention. Paired *t* test was used and Spearman correlation coefficient, *r*, was estimated.

**Results:** Mean age was 37 years (range 16-65 years). Mean serum concentrations of carbamazepine, clobazam, and valproate were significantly reduced after 4 and 12 weeks of the diet period ($<.001 \leq P \leq .02$). Levels of lacosamide, lamotrigine, and topiramate were less reduced ($.02 \leq P \leq .08$), whereas the serum concentrations of oxcarbazepine, zonisamide, and levetiracetam were unchanged ($.06 \leq P \leq .90$). The largest reduction in serum concentration was found for clobazam: mean reduction after 12 weeks was 1.5 μmol/L (34%). Percent change in serum concentration after 4 and 12 weeks of all drugs analyzed was −10.5% (95% confidence interval [CI] −14.1 to −6.8; n = 60; $P < .001$) and −13.5% (95% CI −18.8 to −8.3; n = 56; $P < .001$), respectively. Percent change in serum concentration of AEDs was not significantly correlated to percent change in seizure frequency after 12 weeks of dietary treatment ($r = .14$, $P = .33$, n = 53) but negatively correlated to urine ketosis ($r = -.43$; $P = .003$; n = 46).

**Significance:** A reduction in AED serum concentrations may counteract a seizure-reducing effect of the diet, and in patients without such an effect, it may cause seizure aggravation. Thus, we recommend that clinicians who are treating patients with ketogenic diets monitor serum concentrations of the concomitant AEDs.

**KEYWORDS**

adults, antiepileptic drugs, epilepsy, ketogenic diet, ketosis, serum concentration

## 1 | INTRODUCTION

The ketogenic diets, including a variant of the diet called the modified Atkins diet, are treatment options for children and adults with drug-resistant epilepsy.[1,2] In a recent randomized controlled trial comparing seizure frequency in adults using the modified Atkins diet as add-on to antiepileptic drug (AED) treatment versus no change in current treatment, we found a small beneficial effect of the diet.[3] Of interest, we discovered a reduction in serum concentration of clobazam and carbamazepine, and this might have influenced the results. In addition, in a case report, we presented four adults with a marked reduction of AED serum concentrations after initiation of the modified Atkins diet,[4] suggesting that there may be a pharmacokinetic interaction between AEDs and the diet. To our knowledge, this has not been studied previously in adults.

The aim of this study was to examine the potential impact of the modified Atkins diet on serum concentrations of AEDs in data from adults with drug-resistant epilepsy. The data emanate from investigations on efficacy and tolerability of the modified Atkins diet in adults reported earlier.[3,5]

**Key Points**

- This trial examined the influence of the modified Atkins diet on serum concentration of concomitant antiepileptic drugs in adults with epilepsy
- It was a prospective study; the dietary treatment lasted for 12 weeks
- We found a significant reduction in mean serum concentrations of carbamazepine, clobazam, and valproate, whereas the concentrations of levetiracetam were unchanged
- We found a significant negative correlation between the reduction in AED serum concentrations and the extent of ketosis

## 2 | METHODS

### 2.1 | Study design

In a randomized clinical trial (RCT) of patients with drug-resistant focal epilepsy,[3] 37 patients were randomized to diet while 38 were allocated to a control group. The latter was offered dietary treatment after the intervention period using the same protocol as for the diet group. The results of dietary intervention from both groups are included in the present study. Baseline period is defined as the 12-week period immediately preceding the diet period. Data from a cohort of patients with generalized epilepsy (n = 13) who followed the same protocol of dietary treatment were also included.[5]

These open, prospective studies were performed at the National Centre for Epilepsy in Norway, a tertiary referral center. It was approved by the Regional Committee for Medical and Health Research Ethics in South East of Norway (number 2010/2326). As part of the screening for eligibility, the candidates received oral and written information about the study. Written informed consent was obtained from all participants. The trial was registered with ClinicalTrials.gov (ID NCT01311440).

### 2.2 | Participants

Between March 1, 2011, and February 28, 2017, a total of 277 epilepsy patients from all over Norway were contacted for possible inclusion in the study. The inclusion scheme is given in Figure 1. Screening and inclusion was performed by a senior neurologist (K.O.N. or E.M.) and a clinical nutritionist (M.K.).

Eligible patients had to be >16 years; have generalized or focal epilepsy according to the International League Against Epilepsy's classification[6]; have at least three countable seizures per month, having tried at least three AEDs, including current treatment; have a body mass index >18.5 kg/m$^2$; and they should be motivated for adhering to the diet and capable of preparing the food and calculating nutrients. Assistance from family or caregivers was encouraged.

Exclusion criteria were pregnancy, use of ketogenic diets in the previous 12 months, change of antiepileptic treatment during the study, psychogenic nonepileptic seizures, status epilepticus the previous 6 months, having undergone resective surgery or vagus nerve stimulator implantation during the previous 12 months, or having comorbidities that contraindicated use of the diet.

In total, 63 participants completed 4 weeks of dietary treatment, of whom 56 completed 12 weeks (Figure 1). Three patients were excluded from seizure count because of incomplete dataset, adverse food reaction, or zero seizures at baseline.

### 2.3 | Procedures

The study consisted of the 12-week baseline period, followed by a 12-week period where participants consumed the modified Atkins diet. Participants were admitted to a short hospital stay, if necessary with caregivers, for data collection before starting the diet period. During the admission, diet instruction was given. The effects of the diet intervention were evaluated during 1-day hospital admissions 4 and 12 weeks after initiation of the diet.

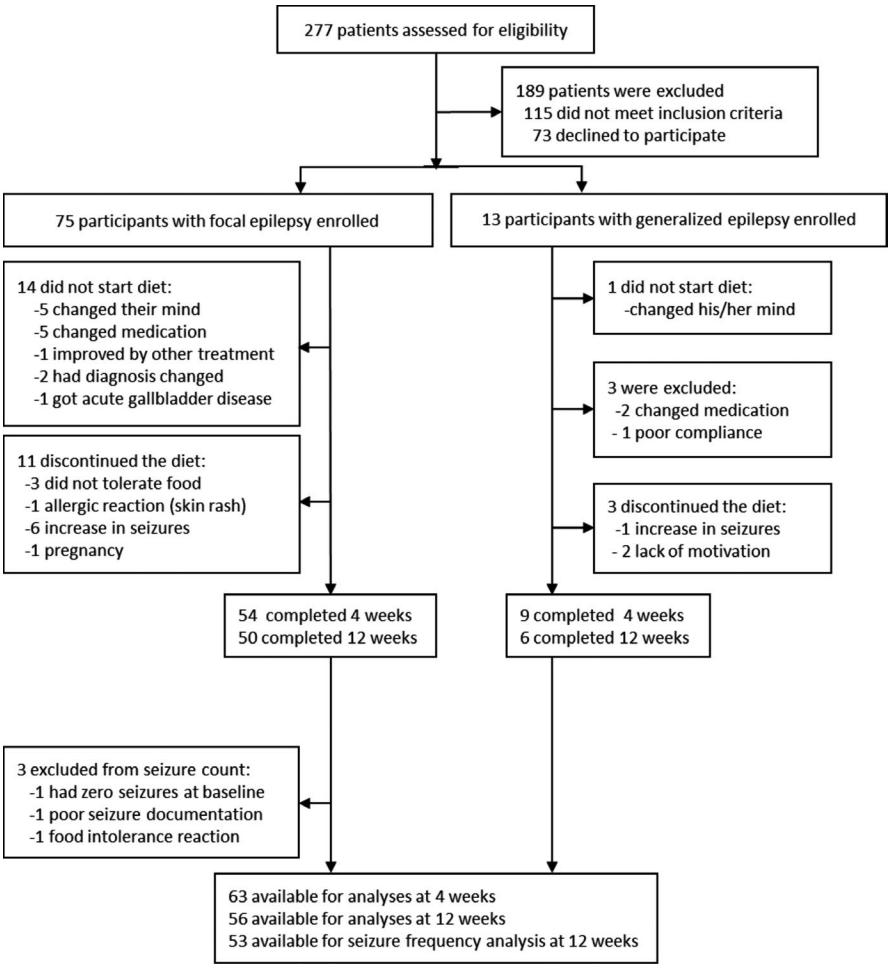


**FIGURE 1** Flow chart illustrating how the study samples were obtained

The concurrent treatment with AEDs and/or vagus nerve stimulation was kept unchanged throughout the study period. If an AED was added or removed, entry into the study (and baseline seizure registration) was delayed by 3 months, whereas if an AED dose was adjusted, the delay was 4 weeks.

Venous blood was collected during admission at 8 o'clock in the morning after a 12-hour (overnight) food and drug fast. We assessed serum levels of AEDs, glucose, 3-hydroxybutyrate, and hemoglobin A1c (HbA1c). The same procedure was employed for all visits. All biochemical analyses were performed by standard methods at Oslo University Hospital. Laboratory methods were available for assessment of serum concentration for the following AEDs: carbamazepine (CBZ), clobazam (CLB), clonazepam (CZP), lacosamide (LCM), levetiracetam (LEV), lamotrigine (LTG), oxcarbazepine (OXC), phenobarbital (PB), pregabalin (PGB), phenytoin (PHT), topiramate (TPM), valproate (VPA), and zonisamide (ZNS). Methods for measuring serum concentration were not available for nitrazepam, tiagabine, vigabatrin, rufinamide, acetazolamide and retigabine, each of which was used by only one or two participants.

To assess diet adherence, participants recorded urine ketosis twice daily during the 12 weeks on the diet using urine dipsticks (Ketostix, Bayer Healthcare, Leverkusen). From these recordings, mean 12-week morning and evening urine ketosis was calculated. In addition, at hospital admissions, ketosis was assessed every morning and evening using urine dipsticks. The morning assessment was based on the very first urination after awakening in the morning, whereas the evening sample was collected immediately before the last meal of the day. Furthermore, the blood concentration of glucose and 3-hydroxybutyrate was assessed twice (morning and evening) based on a fingerprick blood sample using ABBOTT Freestyle Optium Blood Glucose Test Strips and Precision Xtra Blood Ketone Test Strips (Abbott), respectively.

The diet was started at home on a pre-planned date. In agreement with the diet described by Kossoff et al, a maximum of 16 g carbohydrate per day was allowed throughout the study.[7] In the Norwegian Food Composition Database,[8] the amount of carbohydrate specified in foods exclude fibers. Thus, fibers were eaten in free amounts. We encouraged high-fat foods, but did not limit protein or total energy consumption. Medical nutrition products were used as supplements when appropriate. 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.

To evaluate dietary intake, the participants recorded all foods and drinks for 3 days prior to the hospital admissions at the 4- and 12-week time point. Nutritional intake was analyzed using the Norwegian Food Composition Database.[8] Ketogenic ratio is defined as the ratio between fat and protein plus carbohydrate in grams.

### 2.4 | Study outcomes

Primary outcome was a change in serum concentration of each AED from before starting the diet to 4 and 12 weeks of the diet period. Moreover, to evaluate the change of all AEDs taken together, mean percent change of all AEDs was calculated [(after intervention-baseline)/baseline*100].

Secondary outcomes were the proportion of patients who were seizure-free, had >90%, >50% and >25% seizure reduction, and who experienced seizure aggravation after 12 weeks on the diet compared to the baseline period. Additionally, we assessed the average daily intake of energy and macronutrients, dietary ketogenic ratio, change in body weight, urine and blood ketosis, changes in the concentrations of HbA1c, fasting blood glucose, and 3-hydroxybutyrate. We calculated the change (%) in seizure frequency by comparing mean weekly seizure frequency in the baseline period to mean weekly seizure frequency from weeks 5 to 12 in the diet period.

### 2.5 | Statistical analysis

Data are presented as mean (range or 95% confidence interval [CI]), or frequency. Normality of distribution of all the AED serum concentrations was inspected. For AEDs with less than four measurement-pairs, however, the sample size was too small to allow for a meaningful comparison (ie, *P*-values are not given). As for the primary outcome, serum concentrations of drugs after 4 and 12 weeks of the diet period were compared to baseline using a paired *t* test. In addition, a paired *t* test was used to compare the serum concentrations at 4 and 12 weeks of treatment. A one-sample *t* test was used to test mean percent change. A paired *t* test was used to compare weight and metabolic parameters (ketosis, glucose, and HbA1c) after 4 and 12 weeks of diet versus baseline, and to compare metabolic parameters at 4 and 12 weeks of treatment. Missing values are due to errors in connection with sample collection or to missing laboratory analyses. The proportions of patients who achieved seizure freedom and >90%, >50%, and >25% seizure reduction were calculated as mean weekly seizure frequency from baseline to weeks 5 to 12 in the diet period, with 95% CI.[3]

Spearman correlation coefficient, *r*, was calculated to estimate the correlation between percent change in serum concentration of AEDs and percent change in seizure frequency after 4 and 12 weeks of dietary treatment. In addition, to calculate the correlation between percent change in serum concentration of AEDs and weight change, and between percent change in serum concentrations of AEDs (excluding LEV) and metabolic parameters. LEV was excluded because no change in AED serum concentrations from LEV was observed.

IBM SPSS statistics version 25 (IBM) was used for the statistical analyses.

## 3 | RESULTS

Baseline demographic and clinical characteristics of the 63 participants are presented in Table 1A. The ethnicity of the participants was Caucasian, except for one African and one Sami. Dietary intake of energy, fat, protein, and carbohydrate after 4 and 12 weeks on the diet is presented in Table 1B.

**TABLE 1** (A) Baseline characteristics of the 63 participants. (B) Daily dietary intake after 4 and 12 weeks on the modified Atkins diet given as total energy and energy percent (E%) from fat, protein, and carbohydrate, and the intake of fat, protein, and carbohydrate in grams

| **(A)** | |
|---|---|
| Age (y) | 37 (16-65)[a] |
| Female sex | 40 (60%) |
| Epilepsy etiology | |
| Structural | 16 (25%) |
| Genetic | 8 (13%) |
| Infectious | 4 (6%) |
| Unknown | 35 (56%) |
| Age at first seizure (y) | 12 (0-55) |
| Years with epilepsy | 25 (5-58) |
| Intellectually disabled | 23 (37%) |
| Number of AEDs tried | 8.6 (3-23) |
| Number of current AEDs | 2.0 (0-4) |

| **(B)** | **4 wk on diet (n = 54)[b]** | **12 wk on diet (n = 47)[b]** |
|---|---|---|
| Energy, kcal | 1980 (1789-2172) | 1969 (1769-2169) |
| Fat, g | 170 (152-189) | 171 (152-189) |
| Fat, E% | 76 (74-78) | 77 (75-79) |
| Protein, g | 88 (80-96) | 90 (79-101) |
| Protein, E% | 19 (17-20) | 19 (17-20) |
| Carbohydrate, g | 13 (12-15) | 13 (12-14) |
| Carbohydrate, E% | 3 (3-3) | 3 (3-3) |
| Ketogenic ratio | 1.7 (1.6-1.9) | 1.7 (1.5-1.9) |

Abbreviation: AEDs, antiepileptic drugs.
[a]Data are mean (range) or frequency (%).
[b]Values presented as mean (95% confidence interval).

AED use was as follows: 20 used one drug, 21 used two, 19 used three, and 2 used four AEDs. Only one participant did not use any AED. In total, 112 drug samples from 60 participants were available for assessment after 4 weeks, whereas 108 drug samples were available from 56 participants after 12 weeks of treatment. Four-week samples from two participants who completed the 12-week intervention period were missing.

Mean serum concentrations of all drugs with $n \geq 5$ at baseline were reduced after 4 and 12 weeks ($5 \leq n \leq 19$) of diet intervention, except for LEV (Table 2 and Figure S1). The extent of reductions was more evident after 12 weeks than after 4 weeks. All drug changes were statistically significant, except for LCM at 4 weeks, LTG at 12 weeks, OXC at 4 and 12 weeks, TPM at 4 weeks, and ZNS at 4 and 12 weeks. There was no statistically significant change in serum concentrations from 4 to 12 weeks. Details on all drugs, including those with $n < 5$, are given in Table 2.

Percent change in serum concentration after 4 and 12 weeks of all drugs analyzed was −10.5% (95% CI −14.1 to −6.8; n = 60; $P < .001$) and −13.5% (95% CI −18.8 to −8.3; n = 56; $P < .001$), respectively (Figure 2). Similar results were found when excluding those who did not deliver a food record; percent change in serum concentration of all drugs analyzed was −9.6% (95% CI −13.5 to −5.7; n = 54; $P < .001$) and −13.7% (95% CI −19.4 to −8.0; n = 47; $P < .001$) after 4 and 12 weeks, respectively.

For the 27 participants who were randomized to the control group in our previously published RCT,[3] we had two assessments of AED serum concentration, that is, at baseline and after 12 weeks, with no change in treatment. In this period, the mean percent change was −3.3% (95% CI −8.6 to 2.0; n = 27; $P = .21$). Distribution of AEDs was similar to the one in the main analysis.

The mean percent reduction in serum concentrations among those using monotherapy after 4 and 12 weeks on diet were −6% (95% CI −12 to −1; n = 19; $P = .03$) and −12% (95% CI −25 to 1; n = 17; $P = .06$), respectively. When excluding three subjects who used LEV, the mean percent reduction was −8% (95% CI −13 to −2; n = 17; $P = .02$) and −18% (95% CI −30 to −6; n = 15; $P = .006$) after 4 and 12 weeks, respectively.

In nine patients (16%), serum concentrations were reduced with >30% after 12 weeks on the diet. Two of these had a drop of >50%; one used VPA, whereas the other used a combination of CLB and PHT. Of the remaining seven patients, four used CLB in combination with two or three other drugs, two used CBZ alone or in combination with two other drugs, and one used PB as monotherapy. The change in seizure frequency in these nine patients varied from 80% seizure reduction to +278% (ie, seizure aggravation).

The largest reduction in serum concentration was found for CLB; the mean reduction after 12 weeks was 1.5 μmol/L (34%) (Table 2). Of the 10 patients using CLB who completed 4 weeks on diet, 3 had a prominent seizure increase, 3 responded with a reduction in seizure frequency, and the rest remained unchanged.

CBZ, PHT, and PB are known to be strong inducers of the cytochrome P450 (CYP) enzymes. The mean drop in serum concentrations among the participants using one of these drugs after 4 and 12 weeks of treatment was −17.5% (95% CI −24.4 to −10.6; n = 14; $P < .001$) and −20.6% (95% CI −34.7 to −6.5; n = 12; $P = .008$), respectively. Among those not using any of these inducers, the drop was −8.3% (95% CI −12.5 to −4.1; n = 46; $P < .001$) and −11.6% (95% CI −17.3 to −6.0; n = 44; $P < .001$), respectively. Comparison of the two groups after 4 and 12 weeks showed a mean difference in reduction of serum concentrations of −9.2% (95% CI −17.6 to −0.8; n = 12/46; $P = .03$) and −9.0% (95% CI −21.7 to 3.7; n = 12/44; $P = .2$), respectively. After 12 weeks, when excluding one outlier who was using only PHT and who experienced an increase of PHT serum concentration value of 30%, the difference between the groups was −13.6% (95% CI −25.9 to −1.3; n = 11/44; $P < .03$).

After the 12-week diet period, none of the participants were seizure-free. Of those 53 participants available for seizure frequency analysis, none were seizure-free, one (2%) had >90% seizure reduction, 9 (17%) had >50% seizure reduction, and 23 (43%) had >25% reduction of seizure frequency. Five participants (9%) experienced >50% increased seizure frequency, and nine (17%) had >25% increased seizure frequency. Six patients (11%) were unchanged.

We found no statistically significant correlation between percent change in serum concentration of AEDs and percent change in seizure frequency after 12 weeks of dietary treatment ($r = .14$, $P = .331$, n = 53). This estimate was similar after exclusion of the four participants who experienced >90% seizure exacerbation ($r = .12$, $P = .41$, n = 49). Exclusion of participants using LEV (n = 16) gave similar results ($r = .17$, $P = .32$, n = 37).

Mean weight at baseline was 78.5 kg (95% CI 73.5 to 83.5; n = 56) and mean weight change after 4 and 12 weeks of treatment was −2.4 kg (95% CI −3.2 to −1.7; n = 56; $P < .001$) and −4.5 kg (95% CI −3.3 to −5.8; n = 54; $P < .001$), respectively. We found no significant correlation between weight change and percent change in serum concentration of AEDs after 12 weeks of treatment ($r = -.02$, $P = .89$, n = 50). Neither did we find any correlation between dietary ketogenic ratio and ketosis ($r = .16$; $P = .30$; n = 43). However, the variation in ratios was very small, <0.5 (Table 1B).

Changes in ketone levels assessed in urine and blood and blood glucose are given in Table 2 and Figure S2. Ketosis increased significantly from diet start to week 4 ($P < .001$) and from diet start to week 12 ($P < .001$). In addition, there was a decrease from weeks 4 to 12, which was statistically significant for urine ketosis measured in the morning and evening

**TABLE 2** Change in serum concentrations of antiepileptic drugs, ketosis, and glucose after 4- and 12-week treatment with the modified Atkins diet

| | Before diet start | 4 wk on diet | | 12 wk on diet | | 4 vs 12 wk |
|---|---|---|---|---|---|---|
| **Serum concentration** | **n mean (95% CI)** | **change from baseline n mean (95% CI)** | ***P*[a]** | **Change from baseline n mean (95% CI)** | ***P*[b]** | ***P*[c]** |
| CBZ, μmol/L | n = 8<br>36.8 (32.6-41.0) | n = 8<br>−4.9 (−8.7 to −1.0) | .02 | n = 7<br>−8.5 (−12.7 to -4.2) | .003 | .10 |
| CLB, μmol/L[d] | n = 10<br>4.4 (2.3-6.4) | n = 10<br>−1.1 (−1.8 to −0.4) | .007 | n = 9<br>−1.5 (−2.6--0.5) | .009 | .08 |
| CZP, nmol/L | n = 2<br>47.0 (−232.5-326.5) | n = 2<br>−1.0 (−26.4-24.4) | | n = 2<br>−7.5 (−26.6-11.6) | | |
| LCM, μmol/L | n = 6<br>16.7 (10.8-22.6) | n = 6<br>−1.5 (−3.2-0.2) | .08 | n = 6<br>−2.5 (−4.3 to -0.7) | .02 | .40 |
| LEV, μmol/L | n = 16<br>81.6 (58.6-104.8) | n = 14<br>0.6 (−9.7-11.0) | .90 | n = 16<br>3.5 (−5.7-12.7) | .43 | .91 |
| LTG, μmol/L | n = 15<br>27.7 (21.3-34.2) | n = 14<br>−3.4 (−5.7 to −1.2) | .006 | n = 15<br>−3.2 (−6.9-0.5) | .09 | .61 |
| OXC[e], μmol/L | n = 19<br>81.5 (68.9-94.1) | n = 19<br>−2.8 (−9.0-3.4) | .35 | n = 17<br>−7.1 (−14.4-0.2) | .06 | .07 |
| PB, μmol/L | n = 3<br>50.3 (−41.8-142.5) | n = 3<br>−8.0 (−36.0-20.0) | | n = 2<br>−11.0 (−138.1-116.1) | | |
| PGB, μmol/L | n = 2<br>18 (18-18) | n = 2<br>1.5 (−43.0-46.0) | | n = 2<br>4.5 (−1.9-10.9) | | |
| PHT, μmol/L | n = 4<br>42.5 (30.4-54.6) | n = 3<br>−10 (−27.2-7.2) | | n = 4<br>−8.3 (−30.3-13.8) | | |
| TPM, μmol/L | n = 10<br>24.4 (19.6-29.2) | n = 10<br>−3.5 (−7.6-0.6) | .08 | n = 9<br>−4.0 (−7.3 to -0.6) | .03 | .95 |
| VPA, μmol/L | n = 16<br>489 (403-576) | n = 16<br>−85 (−127 to −44) | .001 | n = 15<br>−100 (−142 to -59) | <.001 | .15 |
| ZNS, μmol/L | n = 5<br>78.0 (31.8-124.4) | n = 5<br>−18.4 (−41.0-4.2) | .09 | n = 4<br>−28.1 (−58.3-2.1) | .06 | .06 |
| All drugs[f] change | - | n = 60−10.5 (−14.1 to -6.8) | <.001 | n = 56<br>−13.5 (−18.8 to -8.3) | <.001 | .10 |
| **Ketosis[f] mmol/L** | **n mean (95% CI)** | **n mean (95% CI)** | ***P*[a]** | **n mean (95% CI)** | ***P*[b]** | ***P*[c]** |
| Urine, morning[g] | n = 51<br>0.1 (−0.1-0.3) | n = 48<br>4.3 (3.2-5.5) | <.001 | n = 46<br>2.9 (1.9-3.8) | <.001 | .006 |
| Urine, evening[g] | n = 50<br>0.1 (−0.0-0.1) | n = 46<br>5.3 (4.1-6.6) | <.001 | n = 45<br>3.2 (2.1-4.3) | <.001 | .009 |

(Continues)

**TABLE 2** (Continued)

| Ketosis[f] mmol/L | n mean (95% CI) | n mean (95% CI) | $P^a$ | n mean (95% CI) | $P^b$ | $P^c$ |
|---|---|---|---|---|---|---|
| Blood, morning[h] | n = 52<br>0.2 (0.1-0.3) | n = 52<br>1.4 (1.1-1.8) | <.001 | n = 49<br>1.1 (0.8-1.4) | <.001 | .14 |
| Blood, evening[h] | n = 52<br>0.1 (0.1-0.2) | n = 50<br>1.5 (1.1-1.8) | <.001 | n = 48<br>0.9 (0.6-1.2) | <.001 | .006 |
| Urine daily morning[g,i] | - | n = 50<br>4.7 (3.6-5.8) | - | n = 47<br>4.4 (3.3-5.6) | - | - |
| Urine daily evening[g,i] | - | n = 50<br>6.0 (4.9-7.1) | - | n = 47<br>5.7 (4.5-6.9) | - | - |
| 3-hydroxy butyrate[j,l] | n = 25[i]<br>0.1 (0.0-0.1) | n = 27<br>1.2 (0.9-1.5) | <.001 | n = 28<br>0.8 (0.5-1.1) | <.001 | .02 |
| **Glucose mmol/L** | **n mean (95% CI)** | **n mean (95% CI)** | $P^a$ | **n mean (95% CI)** | $P^b$ | $P^c$ |
| Morning[k] | n = 55<br>5.1 (4.9-5.3) | n = 53<br>4.5 (4.3-4.7) | <.001 | n = 52<br>5.0 (4.8-5.1) | .35 | <.001 |
| Evening[k] | n = 53<br>5.3 (5.0-5.6) | n = 51<br>4.5 (4.3-4.8) | <.001 | n = 48<br>4.8 (4.6-5.2) | .02 | .06 |
| Morning[l] | n = 62<br>5.1 (5.0-5.3) | n = 60<br>4.8 (4.7-5.0) | <.001 | n = 56<br>5.0 (4.9-5.1) | .03 | .001 |
| HbA1c[l], % | n = 63<br>5.3 (5.2-5.4) | n = 59<br>5.1 (5.0-5.2) | <.001 | n = 57<br>5.0 (4.9-5.1) | <.001 | .006 |

Abbreviations: 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]Comparing values at baseline and 4 wk of treatment using the paired *t* test.

[b]Comparing values at baseline and 12 wk of treatment using the paired *t* test.

[c]Comparing change from baseline to 4 wk with change from baseline to 12 wk using the paired *t* test.

[d]Desmethylclobazam, a metabolite.

[e]Eslicarbazepine is analyzed as OXC (licarbazepine).

[f]Variation in n is due to missing values.

[g]Using urine dipsticks, Ketostix.

[h]Using Precision Xtra Blood Ketone Test Strips.

[i]Morning and evening urine ketosis during 4 and 12 wk assessed by patients or caregivers.

[j]The smaller sample size is due to this analysis not being available from the beginning of the project.

[k]Using Blood Glucose Test Strips.

[l]Laboratory assessments.

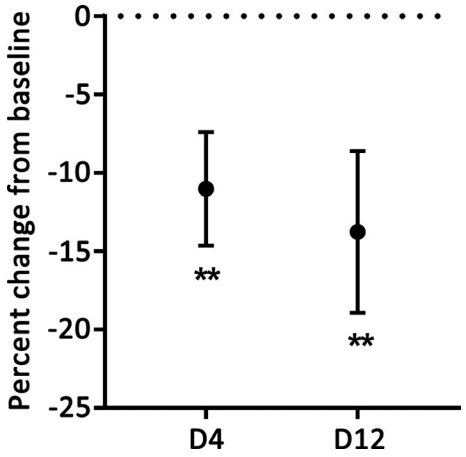


**FIGURE 2** Percent change of all AED serum concentrations taken together (mean 95% CI) after 4 and 12 wk on the diet compared to no change, test value zero is indicated by the dotted line. ** $P < .001$ (significant)

and blood ketosis measured in the evening ($.006 < P < .009$) but not for blood ketosis measured in the morning ($P = .14$) (Table 2 and Figure S2 A-D). Blood glucose assessed in the morning and evening in the ward and at the laboratory in venous blood was significantly reduced from baseline to week 4 on the diet ($P < .001$), and then increased to week 12 ($P = .35$ for morning, $P = .02$ for evening and $P = .03$ in venous blood) (Table 2 and Figure S2 E-G), but not up to the mean level at baseline. HbA1c values decreased significantly from baseline to 4 and 12 weeks ($P < .001$) (Table 2 and Figure S2 H).

We estimated the association between percent change in serum concentration of AEDs and several assessments of urine and blood ketosis, glucose, and HbA1c, measured during admission and at home, morning and evening, and after 4 and 12 weeks of treatment. In the calculations, LEV was excluded. Further details are given in Table S1. Scatter plots of the variables are shown in Figures S3A-C, illustrating how percent change in AED serum concentrations (excluding LEV) correlate with blood ketosis (S3A), self-assessed urine ketosis (S3B), and blood glucose/HbA1c (S3C).

## 4 | DISCUSSION

This is the first prospective investigation of the effect of the adjunctive modified Atkins diet on serum concentrations of AEDs in adults with difficult-to-treat epilepsy. We found a significant reduction in mean serum concentrations of CBZ, CLB, and VPA after 4 and 12 weeks of dietary treatment. The changes in the serum concentrations of LCM, LTG, and TPM were not as consistent, whereas serum concentrations of OXC and ZNS were almost unchanged and LEV was unchanged. Furthermore, the mean percent change in serum concentrations for all drugs pooled together was significant both after 4 and 12 weeks on the diet. The reduction was more prominent after 12 weeks than after 4 weeks, but the change from week 4 to week 12 was not statistically significant. Two subgroup analyses strengthen our findings. (a) Participants who handed in food records may have been more compliant with the diet than those who did not. But when excluding those who did not hand in food records, the change in serum concentrations was very similar to the whole group analysis. (b) In hitherto unpublished data from the previously published RCT,[3] we found no change in serum concentrations of the AEDs in the 12-week period among the 27 patients in the noninterventional group. It strengthens the likelihood that the changes in serum concentration are induced by the dietary treatment.

There are several possible explanations for the reduction of the serum concentration of AEDs. Although it cannot be completely ruled out, nonadherence is in our opinion not likely as the patients were followed closely, with high awareness on keeping drug doses unchanged throughout the study period. Besides, many of them were susceptible to seizures even after having skipped one single dose and were thus highly motivated to adhere.

The ketogenic diets bring about a large number of metabolic changes in the body that may interact with absorption, distribution, metabolism, and elimination of AEDs. Absorption of drugs may be affected by both dietary and other substances. However, given the lipophilic nature of several AEDs, adding more fat to the diet, is expected to increase the absorption and thereby increase rather than reduce the AED serum concentrations.[9,10] Recently, Ahn et al reported that a chelating effect of iron supplement may reduce absorption of CBZ in the elderly.[11] Presumably this was a high-dose iron supplement prescribed to treat anemia. However, bearing in mind the comprehensive change of diet these patients underwent, we cannot rule out that there might have been specific dietary substances introduced by the dietary intervention having a similar effect on our patients, but we have no suspected substances.

A change in the volume of distribution of drugs seems less likely to cause the observed reduction, since a body weight reduction should cause an increase in serum concentration rather than a reduction.

For some of the drugs, for VPA in particular, a diet-induced change in drug-protein binding may play a role, as suggested by Heo.[12] In our study, however, we find this explanation less likely, since there was no difference in aspartate aminotransferase and alanine aminotransferase levels between the diet and control groups.[3] We did, however, not assess change in protein binding.

As fat intake more than doubles with the diet, cholesterol level and bile acid turnover rate are likely to increase considerably, and may upregulate several CYP enzymes that metabolize several AEDs. Their metabolism may be speeded up as a result of the high fat intake, whereas LEV, which is not metabolized in the liver, showed no reduction in serum

concentration.[13] Perhaps strengthening the likelihood of this hypothesis, we found a negative correlation between the reduction in serum concentrations of AEDs and the extent of ketosis, whereas there was a positive correlation between change in AED serum concentration and fasting glucose and HbA1c, respectively. However, the fact that most patients were using two or three drugs makes the interpretation difficult. Nevertheless, we speculate that a changed liver metabolism could be part of the explanation. Moreover, the drop-in serum concentrations of those using the strong CYP enzyme inducers CBZ, PHT, and PB was considerably greater than among those using the other drugs. This further strengthens the hypothesis that there is an interaction of metabolism between nutrients and drugs.

The initial increased ketosis and thereafter a gradual decrease, with the opposite occurring with fasting blood glucose, suggests that a metabolic adjustment takes place between weeks 4 and 12 on the diet. This may reflect an adaption taking into account transcriptional upregulation of enzymes of ketogenic pathways that must be assumed during the 3-4 weeks following such a considerable dietary change. Moreover, we found a negative correlation between the reduction in AED serum concentrations and the level of ketosis, which may indicate that the amount of ketones can play a role in the mechanisms behind the interaction between AEDs and the diet. It is anticipated that the amount of ketones is determined by the ketogenic ratio of the diet: the more fat and less carbohydrate and protein, the more ketones. Our data suggest a dose-response relationship between ketosis and reduction in serum concentration of AEDs; the higher ketosis, the more prominent reduction in AED serum concentration. Thus, one may speculate that a combination of AEDs and diets with lower ketogenic ratio or even the low-glycemic-index treatment could be favorable for some patients.[14]

We would expect that a significant reduction of the AED serum concentrations could counteract the seizure-reducing effect of the diet, and that may have been the case. However, we found no correlation between change in serum concentrations of AEDs and change in seizure frequency. It must, however, be emphasized that the seizure frequency varied considerably between participants.[3] In addition, in some patients like those with highly refractory epilepsies included in this study, a drug may in fact have had no seizure-reducing effect, implying that a reduction in serum concentration of this particular drug did not have any impact on the seizures.

The obvious target when adding ketogenic diets to the existing regimen of AEDs is to achieve an additive or synergistic seizure-reducing effect. Unfortunately, perhaps due to the relatively small number of participants using the individual drugs, we were not able to identify any favorable combinations, but LEV may be a candidate. When combining such ketogenic diets with CBZ, VPA, and CLB in particular, however, there may be a risk of marked reduction in serum concentrations resulting in loss of seizure-reducing effect, or even worse, a seizure aggravation.

Previous studies on this topic are mainly based on children. Dahlin et al found no change in drug serum concentrations of several AEDs after a 12-week follow-up of 55 children on the ketogenic diet.[15] However, there are several major methodologic differences between this study and the Swedish study, making a comparison difficult. (a) There may be differences in drug metabolism between children and adults. (b) Dahlin et al changed the drug doses in many children immediately before diet start and also during the dietary treatment. Moreover, many children in the study by Dahlin et al reduced weight considerably. To compare serum concentrations before and after diet start, a calculation of drug concentration in relation to the dose per kilogram of body weight was made. Our strength is that all medications were kept unchanged throughout the study. Coppola et al found a nonsignificant reduction of serum concentration of VPA after 30 days on diet.[16] Heo et al studied 139 children for at least 30 days on various ketogenic diets and observed a significant reduction in serum concentration of VPA.[12] The reduction in VPA found by Heo et al is in-line with our findings.

The strengths of our study include the relatively large number of patients followed prospectively for 12 weeks on the same diet protocol, the same inclusion/exclusion criteria, and the same data collection methods. Weaknesses are the limited number of patients using the individual AEDs, and the lack of a control group.

In conclusion, our results should act as a reminder for clinicians that AED serum concentrations may be reduced and thus counteract a seizure-reducing effect of AEDs when combined with ketogenic diets. Thus, we recommend close monitoring of the serum concentrations of the adjunctive AEDs in all patients treated with such diets.

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## CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. 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.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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