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Brief Communication

A prospective study of the modified Atkins diet for adults with idiopathic generalized epilepsy

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ABSTRACT

For children with pharmacoresistant epilepsy, the ketogenic diet is an established treatment option worldwide. However, for adults, this treatment is less frequently offered, and its efficacy less well-documented. The aim of this study was to examine efficacy and tolerability of such a diet as an adjuvant therapy to antiepileptic drugs for adult patients with pharmacoresistant generalized epilepsy.

Thirteen patients (12 women) aged 16–57 years were included prospectively. They were treated with a modified Atkins diet for 12 weeks. Nine of the 13 participants had juvenile myoclonic epilepsy (JME), two had childhood absence epilepsy, one had Jeavons syndrome, and one had generalized epilepsy of unknown type.

Six participants, all with JME, completed the 12-week study period. Among these six, four had >50% seizure reduction. Their seizure severity, using the revised Liverpool Seizure Severity Scale, was reduced by 1, 5, 57.5, and 70 points, respectively (scale: 1–100 points). In three of these four responders, quality of life, assessed by QOLIE-89, increased more than 20 points (scale: 0–100 points). Mean reduction of body weight after 12 weeks on diet was 6.5 (range: 4.3–8.1) kg.

Lack of motivation, poor compliance, and seizure aggravation were the main reasons for premature termination of the diet. Apart from one patient who developed gallstones when ending the treatment after 10 months, no adverse effects were noted.

In conclusion, using a modified Atkins diet for 12 weeks led to a clinically relevant reduction of seizure frequency in four of thirteen adult patients with pharmacoresistant generalized epilepsy. All responders were diagnosed with JME. In three of the four, the benefits of diet were so considerable that they chose to continue the treatment.

1. Introduction

The ketogenic diet and the less restrictive variant modified Atkins diet are established treatment options for children with difficult-to-treat epilepsy worldwide. For adults, both ketogenic and modified Atkins diet may be treatment options, but so far, the documentation of effect and tolerability is sparse. Recently, two reviews reported >50% seizure reduction in 29–34% of adult patients treated with the modified Atkins diet [1,2] and that 5–9% of the patients achieved 90% seizure reduction [1]. The diet is claimed to be generally well-tolerated among adults, but adherence to the treatment over time seems to be low [1].

Genetic generalized epilepsies constitute 15–20% of all epilepsies [3,4], of which a majority consists of juvenile myoclonic epilepsy (JME) [5]. Seizures in about 80–85% of those with childhood or juvenile absence epilepsy and JME respond well to antiepileptic drugs (AEDs). Seizures in the remaining 15–20% are drug-resistant [6]. Since epilepsy surgery is not an option in these patients, there is a need for alternative treatment. Interestingly, in the first publication on modified Atkins diet in adults with JME, Kossoff et al. retrospectively reported that 5 out of 8 patients were responders [7].

The purpose of this study was to evaluate the efficacy and tolerability of the modified Atkins diet as an adjuvant therapy to AEDs in adults with difficult-to-treat generalized epilepsy.

2. Method

In this prospective open-label study, patients were consecutively enrolled from March 2011 to September 2014. The study was registered at ClinicalTrials.gov, NCT01311440, and approved by the Regional Committee for Medical and Health Research Ethics (Number 2010/2326). Following 12 weeks of baseline seizure recording, participants were

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treated with modified Atkins diet for 12 weeks. All participants were invited to continue the treatment after the 12-week study period.

2.1. Subjects

Participants were mainly recruited from the outpatient clinic and wards at the National Centre for Epilepsy in Norway. Men and women aged ≥16 years diagnosed with generalized epilepsy classified according to the International League Against Epilepsy [8] were eligible for the study. Further, they should have at least three observable seizures per month, a body mass index > 18.5 kg/m^2, and tried at least three AEDs including current treatment without achieving seizure control, and be motivated for and considered capable of adhering to the dietary treatment. Exclusion criteria were status epilepticus during the previous six months, vagus nerve stimulator implantation in the previous 12 months, prior use of ketogenic diets, psychogenic nonepileptic seizures, pregnancy, and comorbidities that contraindicated the dietary treatment.

2.2. Pretreatment assessments

Inclusion was performed by an epileptologist and a clinical nutritionist. During a baseline period, the participants recorded seizure frequency for 12 weeks while consuming their habitual diet. Immediately before initiation of the modified Atkins diet, the participants were admitted to a short hospital stay for diet instruction and blood sampling.

Body weight examination and venous blood sampling were performed after an overnight food and drug fast. Antiepileptic drugs were administered at 8 pm the evening before blood sampling. We assessed serum levels of current AEDs, biomarkers for hematological function, and lipid and glucose metabolism. All biochemical analyses were performed at Oslo University Hospital using routine assays.

No changes in the AED treatment were allowed during the baseline and diet period. Health-related quality of life and seizure severity were assessed before and after the diet period using the validated questionnaires Quality of Life in Epilepsy Inventory QOLIE-89 (scale: 0–100 points, score increase indicates improvement) [9] and the revised Liverpool Seizure Severity Scale (scale: 1–100 points, score reduction indicates reduced severity) [10].

2.3. Diet initiation

The 12-week diet period was initiated at home on a preplanned date. According to Kossoff et al. [11], the modified Atkins diet for adults restricts carbohydrates to 15–20 g per day and encourages high fat foods, but does not limit or measure protein or total energy. We limited the intake of carbohydrates to 16 g. According to the Norwegian Food Composition Table, carbohydrates do not include fiber. Thus, the carbohydrates in our diet were limited to those digestible by the small intestine, while fibers were eaten in free amounts. A daily fluid intake of at least 2–3 l was recommended. One multivitamin tablet ("Multi", Nycoplus, Takeda) and 800 mg calcium from pure calcium carbonate (Takeda, Asker, Norway) were supplemented daily from diet initiation. Urine ketosis was assessed twice daily with urine dipsticks (Ketostix®, Bayer Healthcare, Leverkusen, Germany) in the morning from the first urine specimen and in the evening before the last meal of the day.

Throughout the 12-week diet period, the participants recorded daily seizure type and frequency.

2.4. Evaluation

The effects of the diet intervention were evaluated during short hospital admissions 4 and 12 weeks after initiation of the diet. We calculated the relative change (%) in seizure frequency by comparing mean weekly seizure frequency in the baseline period to mean weekly seizure frequency from week 5 to 12 in the diet period. Average urine ketosis was calculated from the twice daily self-assessed recordings during the 12 weeks on diet. During the hospital admission, the extent of blood ketosis was measured as the concentration of 3-hydroxybutyrate based on a finger-prick blood sample obtained twice (morning and evening) and using Precision Xtra Blood Ketone Test Strips (Abbott, Alameda, CA, USA). Macronutrient intakes and a ketogenic ratio were obtained from a 3-day weighed diet record in week 10 of the 12-week diet period. Diet analysis was based on the Norwegian Food Composition Tables of 2006 and 2012. The ketogenic ratio was defined as the ratio between the intakes of total fat (g) and the sum of carbohydrates (g) and proteins (g).

2.5. Statistical analysis

Data were analyzed using the Wilcoxon signed-rank test for non-parametric and Student's t-test for parametric, continuous variables. All analyses were performed using IBM SPSS Statistics (IBM Corporation, New York 10504–1722, United States) version 21. Statistical significant differences were assumed for p-values less than 0.05.

3. Results

Demographic and clinical data of the participants along with duration and efficacy of the diet are summarized in Table 1. Mean (range) age at seizure onset was 9 (0–19) years. The mean number of previously tried AEDs was 6 (1–12), while the mean number of AEDs currently in use was 2 (0–3). Nine of the patients had JME. Two had a vagus nerve stimulator implanted in 1997 and 2005, respectively. The mean age of the participants was 36 (16–57) years.

3.1. Effect of diet on seizures and quality of life

The mean duration on diet was 263 days (range: 0–930, median: 75). Of the 13 patients, one never started, one terminated after two weeks, and two patients were later excluded because of poor compliance to the diet and change of AED dose, respectively. Thus, after four and twelve weeks of intervention, nine and six participants, respectively, completed the study and were available for data analyses (Fig. 1). Four participants stopped prematurely because of lack of motivation, while one stopped due to seizure aggravation. One participant had a transient seizure increase during the initial 2–3 weeks, but seizures later responded well and eventually the patient became seizure-free. Four experienced >50% seizure reduction in weeks 5–12. The mean age of those who completed the 12 weeks on diet was 44 (38–57) years.

Among the six patients who completed the study, the mean change in seizure severity was −19 (−70–0). A considerable change (57.5 and 70 points) was measured in two participants who either stopped having generalized tonic–clonic (GTC) seizures or had milder GTC seizures with shorter postictal periods.

In the six patients who completed the 12-week diet period, mean overall quality of life improved by 13 points (2–23). The three responders who later continued the diet each experienced more than 20 points of improvement.

3.2. Dietary parameters and ketosis

Among those who completed the 12-week diet period, the mean dietary ketogenic ratio was 1.5:1 (range: 1.1:1–2.0:1, median: 1.4:1) in week 10. The mean daily energy intake was 1460 (range: 750–1800, median: 1600) kcal comprising a mean protein intake of 66 (range: 36–90, median: 64) g, a mean fat intake of 125 (range: 61–155, median: 145) g, and a mean digestible carbohydrate intake of 14 (range: 13–18, median: 14) g. The average morning urine ketosis (self-assessed) during the 12 weeks on diet was 4.3 (range: 0.5–9.1, median: 3.7) mmol/l. The mean evening urine ketosis was 5.0 (range: 1.0–10.5, median: 3.5) mmol/l.