A pilot trial with modified Atkins’ diet in adult patients with refractory epilepsy

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Received 16 January 2008; received in revised form 2 May 2008; accepted 13 May 2008

Abstract

Objectives: At Ghent University Hospital, the feasibility and efficacy of the modified Atkins’ diet was evaluated in adult patients with refractory epilepsy. The Atkins’ diet restricts carbohydrate intake and was originally designed for weight loss.

Patients and methods: During a 6-month trial period, a carbohydrate restriction of 20 g/day was in place. During a 36 h hospital admission, patients were instructed about the diet. Patients underwent clinical neurological testing, EEG, ECG, blood and urine analyses and mood evaluation before and during the trial. Seizure frequency and side effects were recorded in seizure diaries and followed up at monthly clinic visits.

Results: Eight patients were included in the study. Three out of eight patients followed the diet for 6 months. One out of three patients showed a >50% seizure reduction, 1/3 > 30%, and 1/3 < 30%. Side effects such as constipation and diarrhoea were mild and occurred mainly during the initial week of the diet. Patients reported improved concentration and well being. This was confirmed by improved scores on the Beck Depression Inventory Scale.

Conclusion: This pilot study shows that the modified Atkins’ diet is feasible in an adult population, and that seizure frequency reduction is possible. The results need to be confirmed in larger prospective, controlled studies with comparison groups.

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Keywords: Modified Atkins’ diet; Refractory epilepsy; Ketogenic; Adults

1. Introduction

In 1921 Wilder proposed the ketogenic diet as a treatment for epilepsy. Most often now it is used in children with severe and refractory epilepsy. Recent studies have shown efficacy in adolescents and adults [1,2]. The aim of the dietary therapy is to mimic starvation, as studies in the past have shown anti-epileptic effects under such conditions [3]. The diet encourages the intake of excessive amounts of fat. In order to induce the production of ketones, the diet proposes daily meals containing 80% fat, 15% protein and 5% carbohydrates. This is the so called 4:1 (fat:non-fat) diet [4]. The body is forced to find an alternative energy source due to carbohydrate restriction. Stored body fat is transported to the liver where it is metabolized. As a final product, ketones are released into the circulation and used in the brain as an alternative energy source.

Various hypotheses on the mechanism of action of the ketogenic diet in epilepsy have been proposed [5,6]. The presumed correlation between seizure reduction and ketone increase remains unproven.

With regards to the efficacy of the ketogenic diet, 1/3 of patients are reported to show a >90% reduction in seizure frequency with seizure freedom occurring in 10–15% of patients [7]. Infantile spasms, myclonic, atonic and tonic-clonic generalised seizures are reported to respond favourably to the diet in comparison to complex partial seizures (CPS) [7]. In cases of early epileptic and myoclonic encephalopathies, the diet has not been effective [8].
Due to its restrictiveness, compliance with the ketogenic diet is challenging and requires accurate measurement of daily food intake.

Mild and transient side effects, consisting of constipation, sleepiness, and nausea occur usually during the first weeks of the diet [2,9]. In some patients, hypoglycemia, kidney stones, acute pancreatitis, cardiomyopathy and death have been reported [9,10].

Initiating the diet requires hospital admission and daily counselling. During the diet patients are closely monitored and long-term follow-up is desirable [7]. Intake of calcium, iron and vitamin supplements is mandatory [7].

The Atkins’ diet was developed in the United States in 1970 by Dr. Atkins for the purpose of weight loss. This diet also encourages the intake of fat and the restriction of carbohydrates. In contrast to the ketogenic diet, it does not restrict protein intake or daily calories. The Atkins’ diet allows meals containing 60% fat, 30% protein and 10% carbohydrates [4]. Because of strong carbohydrate restriction, patients following the Atkins’ diet also produce ketones [11].

The purpose of the present study was to evaluate the feasibility of introducing the modified Atkins’ diet in adult patients with refractory epilepsy and maintaining them on the diet for 6 months. In addition, we observed the effect of the diet on seizure frequency, mood and EEG.

2. Patients and methods

Patients with refractory epilepsy who fulfilled the inclusion criteria described in Table 1 and signed informed consent were enrolled in the study. Patients taking valproic acid or topiramate were excluded because the ketogenic diet, combined with one of both of these anti-epileptic drugs (AED) was described to be more likely to produce side effects [12]. However, to date no current data are available to support this on a routine clinical basis [13,14]. In this trial vegetarians were excluded, however the modified Atkins’ diet may be feasible for vegetarian patients.

Included patients were admitted for 36 h to the neurol-ogy department at Ghent University Hospital. At the time of admission, patients underwent 24-h of EEG recording with nine electrodes according to the international 10–20 system. A routine ECG recording was performed and baseline blood and urine samples were collected for metabolic screening. Patients were informed about the modified Atkins’ diet and the pilot trial during a 2 h information session and were instructed and trained to perform necessary metabolic testing at home (urinary ketone testing and blood glucose level analyses). Patients completed the Beck Depression Inventory (BDI) to evaluate depression level [15]. Following hospital discharge, patients started the diet at home. During the 6 months trial, daily intake of carbohydrates was restricted to 20 g. Patients were provided with a daily multivitamin and mineral supplement (Forticine®). Twice daily urinary ketosis was checked using Ketostix® to evaluate patient compliance. Three times per week blood glucose level was tested using Glucotouch® sticks to exclude severe hypoglycemia. Once a week patients were asked to weigh themselves. Patients were asked to note all values, as well as daily food intake, seizure occurrence, and side effects, in specifically designed monthly diaries.

Once a month patients received a phone call from the investigators to check for problems concerning the diet. Once a month patients were seen at the epilepsy clinic. During this consultation, a routine EEG and ECG were performed. Blood and urine samples were collected. Anti-epileptic drugs were kept unchanged during the diet period and AED blood levels were obtained at every clinic visit.

At 6 months, patients were readmitted to the hospital for 36 h. The studies performed initially were repeated. Patients were asked about their wish to continue or to stop the diet.

2.1. Seizure frequency

On the basis of the patients’ personal seizure diary a mean monthly seizure frequency over the 6 months preceding the study was calculated. For patients who completed the full study period of 6 months, seizure frequency during the final month of the study was compared to the baseline seizure frequency.

For patients who remained on the diet for at least 3 months, mean monthly seizure frequency during the diet was calculated and compared to baseline mean monthly seizure frequency. For the group analysis, mean monthly seizure frequency of all patients before and during the trial was com-

<table>
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<th>Table 1</th>
<th>Inclusion- and exclusion criteria for admittance in the study</th>
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| **Inclusion criteria** | – Patients unsuccessfully treated with at least 2 AED  
– Patients with a mean of at least 2 seizures per month  
– Patients able to note seizure frequency accurately |
| **Exclusion criteria** | – Pregnant patients or patients breastfeeding  
– Vegetarian patients  
– Patients aged <18 years old  
– Patients with known medical history of diabetes mellitus, cerebrovascular disease, metabolic disease or rheumatoid arthritis  
– Patients being treated with Topiramate (TPM) and/or Valproic acid (VPA) and experiencing >10% weight changes caused by this medication |
pared. The mean monthly seizure frequency during the trial was first calculated per patient based on the individual trial duration.

2.2. EEG

The 24 h EEG recordings at the beginning and the end of the trial (patients completing the 6 months) were compared qualitatively and quantitatively by two independent neurophysiologists. For the quantitative analysis interictal epileptiform discharges (IED) during 4 h of EEG were visually evaluated: 1 h during the morning, 1 h in the afternoon and 2 h during sleep. Neurophysiologists were blinded for the patients’ identity and for the order of investigations (baseline or after 6 months of modified Atkins’ diet).

2.3. Mood evaluation

The scores of the BDI were compared per patient at the beginning and the end of the 6 months trial.

This study was approved by the Ethics Committee of Ghent University Hospital on 20/07/2005.

3. Results

3.1. Patient characteristics

Eight patients (5 males, 3 females) signed informed consent to participate in the study. Mean age was 41.8 years (range: 31–55). Patients 1, 2, 5, 6 and 8 had CPS, patients 3 and 4 had CPS with occasional secondary generalisation, and patient 7 had Lennox-Gastaut syndrome (Table 2). Mean monthly seizure frequency in all patients before the diet was 26 seizures per month (range: 4–90). The mean duration of epilepsy was 32.4 years (range: 24–41). Patients were taking an average of 3 (range: 3–5) anti-epileptic drugs.

3.2. Feasibility

Three out of eight patients followed the diet for 6 months and were readmitted to the hospital for the final study visit. One patient never initiated the diet at home. Four out of eight patients stopped the diet early. One patient stopped the diet because of a severe accidental neck trauma after 5 months of dieting. One patient stopped because of severe and repeated vomiting during the first month, and one patient stopped the diet during the second month due to continued headache. One patient stopped the diet during the second month due to socio-familial problems. Mean follow-up in all patients was 102 days (0–180) (Table 2).

Two out of three patients who completed the trial, decided to continue the diet in the future. One patient wanted to stop the diet after 6 months, because of coping problems with the restrictiveness of the diet.
3.3. Treatment efficacy

Comparison of seizure frequency during the final month of the study to baseline seizure frequency, in patients that completed the study, revealed a mean seizure frequency reduction of 42.2% (range: 25–60%) (patient 3: seizure frequency reduced from 41 to 24 seizures (42%), patient 6: from 4 to 3 seizures (25%) and patient 8: from 15 to 6 seizures (60%)) (Table 2).

Mean monthly seizure frequency during the diet compared to baseline in patients following the diet for more than 3 months, showed a mean reduction of 20% (patient 2: mean monthly seizure frequency increased from 16 to 19 (−23%), patient 3: mean monthly seizure frequency increased from 16 to 19 (−23%), patient 6: from 4 to 3 (25%) and patient 8: from 15 to 11 (28%)).

The group analysis revealed a decrease in mean monthly seizure frequency, from 28 seizures per month before the diet to 25 seizures per month during the diet.

3.4. EEG analysis

The results of the EEG analysis are listed in Table 2.

3.5. Blood and urine analysis

At the initial screening none of the patients showed significant abnormalities in blood or urine analysis. Urinary ketones were scored with Ketostix® which have a range of 1–6 corresponding to 1, 5, 15, 40, 80 and 160 mg (acetoacetate)/dl. In the seven patients who started the diet, after an average of 3 days (range: 1–8) urinary ketosis (acetoacetate) in the morning was observed with a mean score of 2.4 (=9 mg/dl) (range: 2–4). In the evening, after an average of 2 days (range: 1–3) the mean ketosis score was 2.9 (=14 mg/dl) (range: 2–5). Urinary ketosis, showed an overall decreasing trend during the diet period.

Patients did not report severe hypoglycemia during the diet.

Patients’ home measurements of glucose and ketones were compared to analyses from the hospital laboratory, and this evaluation showed comparable results suggesting reliable testing at home by patients.

In the four patients who had more than four blood sample laboratory-analysis during the study, the ketone amounts (acetoacetate and β-hydroxybutyrate) in the blood were high compared to normal values (between 0.1 and 0.5 mg/dl). In patients 6 and 8 the values were high over the whole study period.

In 3/4 patients, with at least 3 months follow-up, serum lipids (cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL)) did not change significantly during the diet period. In the 4th patient (patient 8), total cholesterol and LDL steadily increased during the diet. The three patients who finished the study (patient 8 included), showed a mean increase in cholesterol from 191 to 253.3 mg/dl, an increase in HDL-cholesterol from 74 to 82 mg/dl and in LDL-cholesterol from 103.4 to 158 mg/dl. AED blood levels showed no significant changes.

3.6. Side effects and tolerability

Two patients (patients 4 and 7) stopped the diet due to intolerance. Patient 7 reported severe and repeated vomiting compatible with ketotic vomiting. Patient 4 had continuing severe headache and stopped the diet at 52 days. During the first day of the diet, shortly after initiation, patients complained about gastrointestinal problems such as nausea (1/7), diarrhoea (3/7) and constipation (3/7). Three out of seven patients reported feeling weak. Following the early side effects, 6/7 patients, reported improved concentration, well being and fitness. One patient mentioned a more erect posture and one patient reported more fluent speech.

During the first month of the diet, patients lost a mean of 3.9 kg (range: 1–6.8). A clear difference was observed between mean weight loss in patients who followed the diet for a short time and those who followed the diet for at least 5 months (respectively 1.5 kg (range: 1–2.6) and 5.0 kg (range: 4–6.8)). The four patients who continued the diet for at least 3 months, had a mean total weight loss of 10 kg (range: 8.5–13.5).

3.7. Mood analysis

Mood improved in all patients completing the study. The subjectively reported improved well being was confirmed by the BDI-score (>12 = probably depressed) that decreased in all three patients. In 1/3 patients (patient 6) there was a reduction of 10 points, with a score of 15 decreasing to 5 after being on the modified Atkins’ diet for 6 months. For patient 3, the score decreased from 2 to 1 and patient 8 her score decreased from 5 to 3 (Table 2).

4. Discussion

In this pilot study the modified Atkins’ diet was evaluated prospectively in a group of eight patients as a possible treatment for adult patients with refractory epilepsy. Three out of eight patients (37.5%) completed the trial period of 6 months. During the sixth month, this study showed an average seizure reduction of 42.2%. One patient reported a >50% reduction in seizure frequency after 6 months. In this pilot trial 7/8 included patients suffered from CPS. However it has been described that patients with generalised seizures respond favourably to the ketogenic diet [7].

The currently available data on the modified Atkins’ diet and its effect as a treatment in adult patients with refractory epilepsy, have been reported in a pilot trial and a recent prospective study with 30 adult patients by Kossoff et al. In the pilot study six patients were included, of whom only two were adults (>18 years old). Three out of four children had a
>50% seizure reduction, but the two adults did not show any seizure reduction [16]. In the prospective study the 30 adult patients were advised to restrict their carbohydrate intake to 15 g/day. However food records show that at the end of the first month a mean of 20 g/day were consumed. In this group 33% of patients had a >50% seizure reduction and in five patients AED could be tapered successfully [17]. Three other studies on the modified Atkins’ diet have been conducted in a strictly paediatric population, involving a total of ±54 children [18–20]. Efficacy in these studies was comparable to studies evaluating the ketogenic diet in children and adults. In 30–50% of patients who followed the ketogenic diet for 6 months a >50% seizure reduction was reported [1–3,10].

In our pilot trial one third of the patients followed the modified Atkins’ diet for 6 months. Two out of five patients who preliminary dropped out did so due to reasons unrelated to the diet (trauma and social-familial problems) and 1 patient signed informed consent but never initiated the diet at home.

In the study conducted by Kossoff et al. [17] 47% of adults followed the modified Atkins’ diet for 6 months compared to 63% of adult patients staying on the ketogenic diet for 8 months [1]. In studies examining the modified Atkins’ diet in pediatric populations the drop-out rate ranges between 20 and 50% [18,19]. In the randomized study by Kossoff et al., children who started the study in the 10 g carbohydrate group, followed the diet longer, indicating that the switch from 20 down to 10 g is more difficult than increasing the amount of carbohydrates after 3 months. All parents and patients believed that a 20 g carbohydrate restriction was more tolerable than 10 g [20].

Literature describes the main reasons why patients stop the ketogenic diet early, namely inefficacy (63–84%), restrictiveness (18–25%) and illness (7–12%) [2,3]. The adults in the recent Kossoff study who quit the modified Atkins’ diet did so due to inefficacy (56%) and restrictiveness (38%) [17]. In comparison, studies with anti-epileptic drugs report a retention rate of 60% at 1 year for levetiracetam [21], 23% at 1 year for gabapentin, 46% at 1 year for lamotrigine and 52% at 1 year for topiramate [22].

The one patient in our pilot trial with a >50% seizure reduction was also the only patient with a decrease in IED on the 24 h EEG. Further follow-up of this patient, will show whether this positive result is maintained.

Despite the lack of information on the effect of the modified Atkins’ diet on EEG, the effect of the ketogenic diet on the EEG of children has recently been investigated. Hallböök et al. [23] found that the number of IED on the 24 h EEG of 18 children was significantly decreased, especially during sleep. This group also found a significant correlation between the reduction in IED and the reduction in clinical seizures. Remahl and colleagues evaluated the 24 h EEG of 23 children before and after 3 months of ketogenic dieting. For 13/23 patients the EEG improved in terms IED that showed a significant decrease. However, this group did not find a correlation with seizure reduction [24]. Other groups have reported on the overall pattern of routine EEG’s in children before and during treatment with ketogenic diet and in the majority a general improvement of the EEG is reported [25–27].

In this pilot trial, urinary ketosis with an evening average of 14 mg/dl (acetoacetate) was achieved in an average of 2 days (range: 1–3). Early during the diet patients reported urinary ketosis of 80–160 mg/dl, but these values could not be maintained. These initial values are comparable with the values that are maintained during the ketogenic diet [2,10] and the results reported by Kossoff on adults following the modified Atkins’ diet. Sixty-one percent of adult patients had moderate-to-large ketosis (60–160 mg/dl) at month 1, but at 6 months this was the case for only 13% of patients [17]. Seventy-four percent of the children in the trial of the modified Atkins’ diet performed by Kossoff, showed a urinary ketosis of 80 mg/dl but this value could not be maintained [16]. Kossoff et al. in a larger study of the modified Atkins’ diet, found that all children had moderate urinary ketosis within 4 days (mean: 1.9 days, range: 1–4 days), but concluded that ketonuria during the modified Atkins’ diet could not be correlated with seizure reduction [18]. Kang did not test urinary ketosis on a regular basis but reported low urine ketones [19].

During this study, blood ketosis was monitored monthly and showed increased values compared to baseline. β-Hydroxybutyrate was consistently higher than acetoacetate, but values were low and beneath what is usually considered the therapeutic level of 30 mg/dl [28].

The ketosis in the classic ketogenic diet is established during an initial fasting period, and afterwards the diet is adjusted in a patient-specific way. The aim is to achieve a stable urinary ketosis of 80–160 mg/dl [2,10]. In the small number of published reports on the modified Atkins’ diet, authors always reported lower urinary ketosis value compared to the values maintained during the ketogenic diet [16,19].

Sirven et al. [1] reported, in a study on the ketogenic diet in adult patients, that despite high values of urinary ketosis the adult patients showed no seizure reduction. In addition, the 20 children in Kossoff’s larger study, who had an initial high urinary ketosis but afterwards lost these high levels, did not show an increase in seizure frequency after the initial reduction [18]. During the randomised trial, no differences in ketosis could be found between the two groups [20].

Moreover, studies have shown that the ketogenic diet can be tapered with loss of urinary ketosis level while maintaining the achieved seizure frequency reduction [6]. These arguments suggest that despite the fact that ketosis is often correlated with seizure control, urinary ketosis alone cannot explain the seizure reduction in adult patients. Only Kossoff et al. [17] could show a slightly, early correlation between the level of ketosis and efficacy in their adult population. This correlation was lost at later time period.

In our study even though ketosis values were lower than those reported during the ketogenic diet, they were good measurements for checking compliance with the modified Atkins’ diet. In fact throughout different studies, ketonuria seems the
most non-invasive and cost-effective means of documenting adherence to the regimen [29].

In some of our patients serum lipids changed during the diet, but not dramatically. The patient with the greatest seizure reduction and EEG improvement during the diet, also showed the largest increase of total cholesterol and LDL. Possible correlation between a change in serum lipids and an anti-epileptic effect has to our knowledge not been reported by others.

The modified Atkins’ diet is a diet allowing high fat intake. Experts in the metabolic field have been very sceptical towards this diet, and expected that lipids would increase dramatically. Two randomised studies were performed [30,31]. Short term results (<6 months) showed that patients who followed the carbohydrate-restrictive diet lost more weight. After 3 months no differences in low density lipoprotein were found between the different dietary groups. High density lipoproteins and triglycerides respectively went up and down, but after 6 months no differences were reported. These results should be interpreted with caution due to relatively short observation periods (3–12 months) and relatively small observation groups (n = 63, n = 132).

Our patients lost a mean weight of 10 kg (range: 8.5–13.5) over the 6 months of the diet. The children following the modified Atkins’ diet in Kossoff’s study, did not show major weight loss unless the children were obese [16,17]. Kang et al. reported a decrease in body mass index (BMI) in 14 children from 18.6 to 17.7 [19]. Five of eleven adult patients in the first Sirven study lost weight [1]. In a second study (study population of 26 patients) patients lost a mean of 6.7 kg (+6.8–28.7) [32]. Kossoff et al. [20] could not find any difference in weight loss between the two groups of the randomised 10 and 20 g carbohydrate study. In studies evaluating the efficacy of diets restricting carbohydrates, a mean weight loss of 5.8 kg is seen in obese patients [31].

All three of our patients, who followed the diet for 6 months, mentioned feeling better, and reported improved concentration and fitness. Two out of three of these patients decided to continue the diet (the two patients experiencing the optimal efficacy: 41.5% and 60% seizure reduction). One of these patients walks with a more erect posture and the other one speaks more fluently. Moreover, the BDI-scores decreased in all three patients completing this 6 months trial. To our knowledge no data have been published in the past on mood/depression surveys and the modified Atkins’ diet. However there have been reports on mood and the ketogenic diet. Remahl et al. [24] performed a visual analogue scale to estimate changes in quality of life (QOL) and found improvement after 3 months of ketogenic diet in 15/23 children. Hallbök et al. [23] tested the effect of the ketogenic diet on QOL and attention (based on visual analogue scales) and also found significant improvement. Both studies stressed the fact that mood changes were not correlated to improved seizure control nor to EEG changes [23,24]. This is in contrast to the results of a study investigating the changed BDI-scores following epilepsy surgery in patients with TLE. The authors found greater decreased depression scores in surgically treated patients and this was correlated to improved seizure control and not to surgery per se [33].

Hallbök et al. correlated improvement of attention to increases in β-hydroxybutyrate blood levels after 3 months of ketogenic diet [23]. During our pilot trial, blood ketosis was monitored monthly and showed increased values compared to baseline and was consistently higher than acetooacetate. In this small patient group correlations with attention were not feasible.

Several studies reported on patients with improved cognition or general well being. Sirven et al. [1] mentioned one adult patient who followed the ketogenic diet and had a <50% seizure reduction but continued the diet because of improved cognition. All together, 64% patients in the Sirven study versus 86% in our pilot study, reported improved cognition. These positive side effects cannot be explained by reductions in AED doses, like Coppola did [2], because AED doses were not changed during the diet period in the above described studies. In our pilot trial this was confirmed by stable AED blood levels.

It is evident that dietary treatment may induce a placebo effect. Kossoff and co-workers [3] observed in their study of the ketogenic diet in adolescents, that patients depending on their parents had longer follow-up but less efficacy. This finding can be explained by a wearing off of the placebo effect, but a non-placebo therapy could also wear off. A meta-analysis for placebo effect in randomised trials for AED revealed that 9.3–16.6% of patients in the placebo arms of the studies, showed a >50% seizure reduction [34]. The modified Atkins’ diet requires focused and continuous attention, and therefore could have a psychological effect at least as potent as a placebo drug. Designing a protocol to correct for this bias is a challenge. One approach might be to divide the study population in two treatment groups. One group would receive complete information about the aims and the goals of the study and would be asked, in addition to follow the diet, to perform blood and urine tests at home. The second group would only receive the minimum information that is necessary for the diet and would not do blood and urine tests at home. Differences in efficacy of the diet between the two groups could be a marker for psychological influences.

Despite the small population in this pilot trial, our results confirm the earlier but few reported results and show that seizure reduction can be obtained in adults following the modified Atkins’ diet. Moreover improved mood and well being was observed in the majority of patients following the modified Atkins’ diet.

Acknowledgements

Professor Boon is a Senior Clinical Investigator of the Fund for Scientific Research-Flanders and is supported by grants from the Fund for Scientific Research–Flanders (FWO); grants from Ghent University Research Fund, and by
the Clinical Epilepsy Grant from Ghent University Hospital 2004-2008. Dr. K. Vonck is supported by BOF-ZAP mandate and Dr. V. De Herdt is supported by junior researcher (“Aspirant”) grant from the Fund for Scientific Research–Flanders.

“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


