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Ketogenic diet treatment in adults with refractory epilepsy: A prospective pilot study

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SUMMARY

Purpose: To assess the efficacy of ketogenic diet (KD) in adults with refractory epilepsy.
Methods: Eligible subjects were 18–45 years old with at least two monthly focal seizures (with or without secondary generalization) documented by 8 weeks' follow-up. Classic form of KD treatment (90% fat) was planned for 12 weeks: daily seizure diaries were kept and measurements of the urinary ketones were recorded. Blood studies were done monthly and resting energy expenditure (REE), substrate utilization; body composition and quality of life (QOL) were measured before and after intervention.
Results: Nine patients were enrolled (average age 28 ± 6 years; seven women). Only two subjects concluded the study per protocol due to an early drop-out. The average length of KD treatment was 8 ± 4 weeks (two patients completed 12 weeks of KD; feelings of hunger and lack of efficacy resulted in withdrawal of the rest). The two patients who concluded the study had a more than 50% reduction in the frequency of the seizures. The others experienced no improvement. Adherence to the KD protocol (100%) was documented by constant ketonuria and increased fat utilization as indicated by the change in respiratory quotient ($p < 0.031$). The KD increased the cholesterol levels (mainly LDL; $p = 0.0001$).
Conclusions: In our experience with relatively small adult population, adherence to KD is difficult. In patients who had compliance over 3 weeks (6/8), KD does not seem to have a significant effect. Yet, the significant reduction in the two patients who concluded the study per protocol may indicate that some patients may benefit from this diet. Significant increase in LDL levels and the unlikable dietary changes are additional impediments to its implementation among adults with refractory epilepsy.

Introduction

Considerable progress in understanding the pathophysiology of epilepsy and its treatment has been made over recent years. Despite the development of new drugs, invasive devices and the ability to resect epileptic foci, epilepsy remains refractory to treatment in about 30% of the patients.[1] These patients face a future with a severe and chronic disease manifested by uncontrolled seizures that can significantly affect their quality of life (QOL) and their mood as well as interfere with their ability to work and to conduct a normal social life.[1] Alternative effective treatment modalities are urgently needed. The development of a ketogenic diet (KD) for the treatment of epilepsy followed the observation that fasting could induce seizure control. Once a major therapeutic modality in epilepsy, its implementation decreased with the introduction of drug treatments, and it is currently reserved mainly for children with uncontrolled seizures.[2,3] There are several KD protocols,[2,4] and all are based on lipids, rather than carbohydrates, as the main source of energy to the body. The calculation of the daily caloric intake in the classical KD is based on the age and gender of the subjects and the diet is constructed to supply very high amount of fat and very low amount of carbohydrate (ratio 3:1) and with close to normal protein content.[2,4] It is assumed that the ketone bodies that are formed during the diet play a major role in seizure control.[2,4]

The efficacy of KD treatment in epilepsy is mainly known from observational studies. A Cochrane review found that there is no reliable evidence from randomized controlled trials to support the

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use of ketogenic diets for people with epilepsy. However, based on the results of several large cohort studies the authors concluded that "in those who have a difficult to control epilepsy on multiple modern antiepileptic drugs, we consider a ketogenic diet a valid option".[5] These studies report that a significant seizure control can be achieved in children treated with KD, reaching a greater than 50% reduction in the frequency of the seizures in more than half of them.[2] In the largest reported prospective study, out of 150 children treated with KD, 3% were seizure free after 3 months, 31% gained more than 90% reduction in their seizure frequency and 26% had 50–90% reduction in the frequency of the seizures.[3]

In adults, on the other hand, the practice of KD in the treatment of epilepsy is uncommon and its efficacy in this age group is practically unknown. Almost eight decades ago, Barborka[6] reported that among 100 adults treated with KD for epilepsy, 12% were seizure free after 1 year and 44% had significant improvement. Contemporary information is very sparse. In their small case series, Sirven et al.[7] reported that 3 out of 11 patients with refractory epilepsy gained 90% frequency reduction and another 3 patients had a 50–89% frequency reduction after 8 months of KD treatment. In one 20-year-old patient with refractory epilepsy, Schiff et al. reported that KD treatment reduced the seizure frequency from daily seizures to 5–7 in 1 month.[8]

The current prospective pilot study aimed to evaluate the efficacy and tolerability of KD treatment in adults with refractory epilepsy. We also assessed the influence of the KD on their lipid profile, energy expenditure and body composition as well as on their QOL.

Methods

This was an open prospective study. The research received prior approval by the ethical committee of our institution.

The study population

Subjects were recruited from our outpatient epilepsy clinic. After they signed informed consent, we included males and females 18–45 years old who were diagnosed as having epilepsy with focal seizures with or without secondary generalization for at least 2 years. Each had $\geq$2 seizures monthly in spite of treatment with at least three major antiepileptic drugs at therapeutic levels. We included patients in whom the KD requirements could be ascertained being independent or helped by a caregiver. Exclusion criteria were current treatment with topiramate or acetazolamide, concurrent diabetes mellitus, arterial hypertension, cerebrovascular and peripheral vascular diseases, abnormal electrocardiogram, history of hyperlipidemia or chronic kidney or liver disease or known inherited metabolic disorder.

Study procedure

Patients who met the inclusion criteria completed a baseline daily seizures diary for 8 weeks (with the help of family members when needed). Assessment of caloric intake, including the contribution of the different macronutrients, over the last 2 months was done by a certified clinical nutritionist experienced with KD treatment in children and using retrospective recall data as well as prospective 3-day food records. Classic form of KD treatment (90% fat) was planned for 12 weeks. The KD treatment was begun with 1 week of gradual induction until reaching medium-high levels [50–150 mg/dl (5–15 mmol/L)] of ketonuria (early morning self assessment; Choiceline 10, Roche). Daily seizure diaries were kept and measurements of the urinary ketones were recorded. Efficacy was established as equal to or >50% seizure reduction compared to baseline seizure frequency.

Ancillary studies

Lipid levels, electrolytes, liver and kidney functions were assessed at baseline and every 4 weeks during the treatment period and 4 weeks post-treatment (or when the patients withdrew from the study). Resting energy expenditure (REE) was measured by an open-circuit indirect calorimeter (Deltatrac, Helsinki, Finland) in order to assess the effect of the diet on energy needs. Patients fasted (water drinking was allowed) from 20.00 h the night preceding the test which was carried out the next morning. They lay supine for 30 min prior to evaluation at 08.00. After calibration with standardized oxygen and carbon dioxide gas concentrations (95% O_2 5% CO_2), a plastic canopy was placed over the patient's head and REE was measured for 1 h. There was a 10-min washout period before starting data collection. The inter-individual coefficient of variation in our laboratory is <3%. The respiratory quotient (RQ) was determined based on the above measurements (RQ value of 1 indicated exclusive carbohydrate utilization while RQ of 0.7 indicated exclusive lipid utilization).[9] The average RQ of healthy controls in our laboratory is 0.83 ± 0.04.[10]

Fat and lean body mass (fat-free mass) were determined by a dual energy X-ray absorptiometry (DEXA) prior to implementation of the diet and at 3 months in order to assess the influence of the KD on body composition.[11]

The QOL of the patients was evaluated with QOL31, a questionnaire for patients with epilepsy that assesses seven areas: seizure worry, emotional well-being, energy/fatigue, cognition, social function, medical effects and overall QOL.[12] The patients filled in the questionnaire at baseline and at 3 months.

Data were analyzed by paired or unpaired *t*-tests, as appropriate.

Results

Forty-seven patients diagnosed with intractable epilepsy were screened. Twenty (43%) patients did not meet the study criteria (such as fewer than two attacks/month, use of carbonic anhydrase inhibitors) and 18 (38%) patients declined to participate (unwilling to change their diet). Nine (19%) patients were eligible and agreed to enroll in the study but one withdrew from the study during the KD induction week due to diarrhea. The characteristics of the remaining eight patients are given in Table 1. The average age of the participants was 28 ± 6 years, and there were seven females. The average duration of epilepsy was 20 ± 8 years (range 5–27 years) and the patients had a mean of 14 ± 15 (range 2–49) focal seizures in 1 week during the 8-week baseline follow-up. They were being treated by one to three antiepileptic drugs at the time of study entry.

KD treatment

The contribution of the different macronutrients to the diet before and during the study and the average caloric intake are given in Table 2. Total caloric intake tended to increase during the study (1658 ± 613 kcal/day vs. 1916 ± 241 kcal/day) due to feeling of hunger and or documented weight loss, maintaining the basic 3:1 ratio. Ketonuria was achieved in all of the participants during the week of gradual KD build-up and it was kept at medium–high levels during the whole study, except for one patient, probably due to low compliance (Table 1).

The average duration of the KD treatment was 8 ± 4 weeks (average $\pm$ S.D.; range 1–12 weeks; Table 1). An early dropout from

Table 1
Average weekly seizure frequency during baseline follow-up, during KD treatment and average urine ketones level during KD treatment

Patient	Gender	Age (year)	Epilepsy duration (year)	Average weekly seizure frequency at baseline ± S.D. (range)	KD duration (weeks)	Average weekly seizure frequency during KD ± S.D. (range)	Average weekly urine ketones levels during KD (mg/dl)
1	M	36	25	49 ± 31 (12–108)	12	15 ± 5 (7–26)	87
2	F	26	25	2 ± 1 (0–4)	12	1 ± 1 (0–3)	45
3	F	28	27	19 ± 5 (8–28)	11	20 ± 7 (9–32)	9
4	F	36	15	4 ± 2 (0–7)	10	6 ± 6 (0–15)	103
5	F	23	11	4 ± 2 (1–7)	8	3 ± 3 (0–9)	80
6	F	36	24	18 ± 3 (14–24)	6	27 ± 4 (24–33)	126
7	F	26	24	20 ± 18 (10–64)	3	17 ± 1 (16–17)	96
8	F	25	24	3 ± 1 (1–5)	1	7	–

S.D.: standard deviation.

Table 2
Diet composition before and during the study

Macronutrients	Before study	During study	$p<$
Total caloric intake (kcal/day)	1658 ± 613	1916 ± 241	0.44
Carbohydrates (%)[a]	44.99 ± 12.10	2.61 ± 0.07	0.031
Fat (%)	36.40 ± 14.48	87.10 ± 0.02	0.031
Protein (%)	19.07 ± 5.15	10.76 ± 1.05	0.031

[a] Percentage of total caloric intake.

the KD treatment was noted. Causes for eventual study withdrawal were lack of efficacy (patients #4 and #6), feeling of hunger (patient #7), jaw fracture consequent to seizure (patient #8) and hypertriglyceridemia (patient #5).

Seizure frequency

High KD treatment efficacy (>50% seizure reduction) was found in the only two subjects who completed the study according to the protocol. No significant decrease in the seizure frequency was found when we analyzed those subjects who concluded 3 weeks or more of the KD (6/8) (Table 1). These changes were noted after 1–2 weeks of the KD treatment and lasted throughout the entire treatment period. The change in the seizure frequency during the KD treatment or the degree of ketonuria was unrelated to the age or the gender of the patients, nor to the duration of the epilepsy or the baseline seizure frequency (Table 1).

Metabolic tests

Elevated lactic dehydrogenase levels were detected in one patient prior and during the study (425 U/L) and in two other patients during the study (470 U/L, returning to normal value at the post-study test). The electrolytes, kidney and liver functions studies were in the normal range prior and during the study. The average baseline total cholesterol levels were in the upper normal range, with values of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) within normal ranges, permitting study inclusion (Table 3). The KD resulted in a 26% increase of the total cholesterol values after 4–7 weeks ($n = 6$) of treatment and by 33% after 11–12 weeks ($n = 3$). Similarly, LDL values increased by 32% and 54%, respectively, with no change in the HDL levels. Triglyceride levels remained within the normal range except in one patient, in whom a high level (834 mg/dl; normal range 50–175 mg/dl) after 6 weeks on the diet necessitated termination of the diet: his triglyceride levels subsequently returned to normal.

Six patients who completed at least 6 weeks of KD treatment had a mean weight loss of 2.8 kg ± 1 after 4–6 weeks of treatment. These changes occurred despite the increase in the caloric intake and a decrease of 4% ± 2.6 in the REE during the diet compared to the baseline values (Table 4). DEXA studies revealed no change in the lean body mass while on the diet, while the total body fat content decreased by 4% ± 2 compared to the baseline values (Table 4). The respiratory quotient decreased during the diet (0.83 ± 0.04 vs. 0.73 ± 0.02), indicating a higher fat substrate utilization on the KD.

QOL

The patients' baseline QOL score was low, averaging 42 ± 17, and it remained in the lower range (51 ± 22) in the six patients who had 8 ± 2 weeks of treatment. Three subjects (patients #2, #3, and #5) had an increase in their QOL, mainly due to increased cognition (alertness and concentration), while either no change or a decrease in the QOL was noted in the other five. The changes in the QOL were unrelated to the accompanying changes in the frequency of the seizures.

Discussion

KD in adult patients with epilepsy seems to be hard to perform as indicated by the high rate of dropout in our study. High KD

Table 3
Lipid profile

	n	Total chol. av. ± S.D. (range) (mg/dl)	LDL av. ± S.D. (range) (mg/dl)	HDL av. ± S.D. (range) (mg/dl)	Triglycerides av. ± S.D. (range) (mg/dl)
Normal range (mg/dl)		150–200	60–160	35–70	50–175
Baseline	9	199 ± 24(172–236)	115 ± 20 (79–140)	69 ± 24 (44–120)	78 ± 36 (46–158)
4–7 weeks of KD	6	251 ± 52[a] (196–300)	152 ± 38[c] (113–167)	69 ± 22 (45–109)	218 ± 302 (78–834)
11–12 weeks of KD	3	266 ± 25[b] (238–287)	177 ± 20[d] (154–193)	70 ± 6 (62–74)	98 ± 44 (53–140)
5 weeks (av.) post-study	6	207 ± 22 (177–231)	110 ± 28 (77–161)	84 ± 23 (50–115)	67 ± 30 (33–104)

Baseline, in-study and post-study values. chol.: cholesterol; av.: average; S.D.: standard deviation; LDL: low-density lipoprotein; HDL: high-density lipoprotein; KD: ketogenic diet.
[a] $p < 0.02$ compared to baseline.
[b] $p < 0.002$ compared to baseline.
[c] $p < 0.03$ compared to baseline.
[d] $p < 0.0001$ compared to baseline.

Table 4
Changes in anthropometric and nutritional parameters during the study

	Baseline	At 4–6 weeks of KD	$p<$
Weight (kg)	57.9 ± 7.3	55.6 ± 5.5	0.063
BMI (kg/m^2)	20.65 ± 3.03	19.82 ± 2.41	0.063
LBM (kg)	40.42 ± 5.95	40.88 ± 5.25	0.84
Body fat (%)	28.17 ± 9.83	23.77 ± 7.29	0.031
Caloric intake (kcal/day)	1658 ± 613	1916 ± 241	0.44
REE (kcal/day)	1327 ± 88	1272 ± 83	0.031
RQ	0.83 ± 0.04	0.73 ± 0.02	0.031

KD: ketogenic diet; BMI: body mass index; LBM: lean body mass; REE: respiratory energy expenditure; RQ: respiratory quotient.

treatment efficacy (>50% seizure reduction) was found in the only two subjects who completed the study according to the protocol. Since the effect of KD is seen already after 3 weeks of treatment we also analyzed those subjects who concluded 3 weeks or more of the KD (6/8), however, no significant decrease in the seizure frequency was found. Noteworthy, the three patients who maintained the 11–12 weeks protocol were dependent on their family members in terms of food supply. One can assume, therefore, that the dietary limitations imposed by the KD could be an obstacle for independent adults to continue a long-term treatment, while it might be achievable in young children.

The change in the respiratory quotient[13,14] and the high levels of ketonuria (except patient #3) indicate the compliance of our patients to the KD and exclude non-adherence. Moreover, the level of ketonuria and the change in respiratory quotient did not correlate with the seizure frequency, and nor did the patients' age, gender and the duration of the epilepsy or the baseline frequency of the seizures.

Three of our patients noted a higher sense of alertness and concentration, a recognized effect of the KD,[2] but overall group QOL did not change to any great extent and remained low. They remained with frequent seizures and disabling disease. In addition, the dietary limitations reduced food enjoyment and added a sensation of hunger. Over one-third (38%) of the patients who met the inclusion criteria refused to participate due to the dietary limitations, despite knowing that no other optional treatment is currently available. The resignation of oneself to a life with epilepsy might interfere with complying with a treatment that demands changes in lifestyle (special food preparation and restricted diet) and therefore not suitable for most independent adults with refractory epilepsy.

These results are vastly different from those reported in the pediatric age range where 3 months of treatment with KD achieved more than a 50% reduction in the frequency of the seizures in 60% of the children.[3] Previous reports on adults also indicated higher efficacy in refractory epilepsy.[7,8] Although in some patients there was a change in the seizure frequency we cannot exclude that these changes are not due to the random fluctuation seen in the disease or to a placebo effect due to the fact that the patients were aware of the type of diet being used. It is also possible that the duration of the epilepsy in our patients contributed to the low effectiveness of the KD treatment.

The metabolic changes which were observed during this study are interesting since in spite of a tendency for higher caloric intake, all of the six patients who completed 6 weeks of the KD lost weight. This weight loss was due to a decrease in body fat mass and not to their lean body mass, as was previously reported in subjects on the Atkins diet.[15] Loss of weight during the diet was also previously described in children under KD treatment.[16] Weight loss in the face of decreased resting energy expenditure and a tendency to higher caloric intake is not easy to explain and may be due to fat malabsorption caused by the high fat content of the diet or to a change in metabolic pathways, similarly to the Atkins diet.[15]

The KD treatment resulted in a considerable and progressive increase, although reversible, of the cholesterol levels (mainly LDL). This previously reported adverse event[17] leads us to reconsider long-term usage of KD in adults. The high levels of cholesterol recorded prior to the study (199 ± 24 mg/dl) may be associated with the usage of carbamazepine by six of our eight patients.[16] No other major changes were noted during the KD treatment, except for a single and reversible increase in the triglyceride value measured in one patient.

The results of this pilot study, in a relatively small population of adults with refractory epilepsy, showed that most of our patients could not adhere with the diet. While the two who completed the study benefited significantly, no significant change was found in the others. A significant increase in LDL levels and unpleasant dietary changes are additional impediments to the implementation of this treatment among adult patients.

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