Modified ketogenic (Atkins) diet as a treatment option for adults with drug-resistant epilepsy

Doctoral thesis by

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SUMMARY OF THESIS IN NORWEGIAN LANGUAGE

Ved Spesialsykehuset for epilepsi får vi henvist pasienter med alvorlig epilepsi fra hele Norge. Til tross for å ha forsøkt flere antiepileptiske legemidler, har de ikke fått kontroll på anfallene. Noen av disse pasientene kan hjelpes med ikke-farmakologisk behandling, slik som epilepsikirurgi eller vagus nervestimulering. Men det er et stort behov for flere og bedre behandlingsalternativer for denne pasientgruppen.

I 2010, før vi startet dette prosjektet, var ketogen diett i ferd med å bli en anerkjent behandling av alvorlig epilepsi hos barn, og mange lurte på om dietten kunne ha en plass også i behandlingen av voksne med vanskelig kontrollerbar epilepsi. På denne tiden var det kun publisert resultater fra fire mindre prospektive kliniske studier hos voksne, og det var stort behov for mer kunnskap.

I 2011 startet vi derfor dette prosjektet med det formål å undersøke effekt og tolerabilitet av behandling med modifisert ketogen (Atkins) diett hos voksne med farmakoresistent epilepsi. Blant voksne med epilepsi har omlag 80 % en epilepsi av fokal type, mens hos rundt 20 % er den av generalisert type. Vi valgte derfor å gjøre et todelt prosjekt: 1) en randomisert kontrollert studie på fokal epilepsi, og 2) en prospektiv studie på generalisert epilepsi.

Den randomiserte kontrollerte studien besto av en 12 ukers basisperiode med anfallsregistrering og normal kost, etterfulgt av en 12 ukers intervensjonsperiode der deltakerne ble tilfeldig trukket til diettbehandling (diettgruppen) eller å fortsette med vanlig kost (kontrollgruppen). Formålet var å undersøke endring i anfallsfrekvens fra basis- til intervensjonsperiode. Deltakerne i kontrollgruppen fikk tilbud om å forsøke diettbehandling etter kontrollperioden, også som en del av prosjektet. Legemidler og annen behandling var uendret gjennom studien.

Den prospektive studien fulgte samme protokoll som den randomiserte kontrollerte studien, men uten kontrollgruppe.

Tidlig i studiens forløp observerte vi et fall i serumkonsentrasjonen av legemidlene etter start av dietten. I 2015 publiserte vi dette funnet basert på fire kasuistikker (Artikkel 1). Samme år publiserte vi en artikkel der vi oppsummerte effekten av diettbehandling hos 13 pasienter med generalisert epilepsi (Artikkel 2); noen oppnådde god effekt.

Inklusjon av deltakere til den randomiserte kontrollerte studien gikk langsommere enn forutsatt, og etter å ha inkludert 75 deltakere bestemte vi oss for å avslutte inklusjonen i 2017. I 2018 publiserte vi hovedresultatene fra denne studien (Artikkel 3). Vi kunne ikke påvise en anfallsreduserende effekt av behandlingen i en «intention-to-treat» analyse, men de som fullførte behandlingsperioden hadde en moderat anfallsreduserende effekt (25 % reduksjon av anfallsfrekvensen) sammenlignet med kontrollgruppen. Det var stor variasjon i effekt av diettbehandlingen; noen hadde ingen anfallsreduserende effekt, andre hadde en moderat effekt, mens noen få hadde svært god effekt.

Artikkel 4 gir en prospektiv analyse av det diettinduserte fallet i serumkonsentrasjonen av de ulike antiepileptiske legemidlene. Vi fant en korrelasjon mellom ketose og fall i serumkonsentrasjoner.

Dette prosjektet har bidratt til ny kunnskap om diettbehandling hos voksne med vanskelig kontrollerbar epilepsi. Vi har funnet at behandling med modifisert ketogen (Atkins) diett i denne pasientgruppen lar seg gjennomføre, og at dietten tåles godt uten alvorlige bivirkninger.

Vi foreslår at behandling med ketogen diett etableres som et behandlingstilbud til voksne med alvorlig epilepsi.

SUMMARY OF THESIS IN ENGLISH LANGUAGE

In Norway, people with severe epilepsy are referred to the National Centre for Epilepsy. Most of them have tried several antiepileptic drugs (AEDs) without achieving seizure control. A few of these may be helped by non-pharmacological therapies like epilepsy surgery or vagus nerve stimulation, but there is an urgent need for more and better treatment options for this patient group.

In 2010, prior to the start of this project, ketogenic diet was emerging as a well-recognised treatment in children with refractory epilepsy, and many wondered if dietary treatment might have a place in the treatment of adults with difficult-to-treat epilepsy. At that time, only four minor prospective studies in adult patients had been undertaken, and there was a great need for more solid knowledge.

Therefore, in 2011, we started a project aiming at exploring the effect and tolerability of modified ketogenic (Atkins) diet in adult patients with pharmaco-resistant epilepsy. Among adults with epilepsy, about 80% have epilepsy of focal type, while about 20% have a generalised type. In line with this, we conducted two project parts; 1) a randomised controlled trial (RCT) of focal epilepsy, and 2) a prospective study of generalised epilepsy.

The RCT included a 12-week baseline period with seizure count and habitual diet, followed by a 12-week intervention period where the participants were randomly drawn to either diet (diet group) or habitual diet (control group). The aim was to study change in seizure frequency from the baseline period to the intervention period. Those allocated to the control group were offered dietary treatment after the 12-week control period. AEDs and other treatments were kept constant throughout the study period.

The prospective study was performed according to the same protocol as the RCT, but without control group.

Early in the course of the study we observed a reduction in the serum concentrations of the AEDs after diet start. In 2015, we published this preliminary finding based on four cases (Paper 1). In the same year we published the results of the effect of dietary treatment in 13 patients with refractory generalised epilepsy (Paper 2); some responded.

Inclusion of patients to the RCT turned out to be slower than anticipated. We therefore decided to stop the inclusion prematurely after having included 75 patients. The main results of the RCT were published in 2018 (Paper 3). In an intention-to-treat analysis we were not able to detect a seizure-reducing effect of the diet, but those who completed the 12-week intervention had a modest reduction (25%) in seizure frequency compared to the controls. If and how the diet impacted the patients' seizures, varied considerably; in some the diet had no effect, in others it had a moderate effect, while in a few patients the diet had an excellent effect.

Paper 4 was about the drop in serum concentrations of the various AEDs, and, we found a correlation between drop in serum concentrations and extent of ketones.

Our project has contributed to novel knowledge within the field of dietary treatment in adults with difficult-to-treat epilepsy. We have shown that treatment with modified ketogenic (Atkins) diet can be accomplished, and that it is usually well tolerated without serious side-effects.

We suggest that ketogenic dietary treatment should be offered to adult patients with severe epilepsy.

LIST OF PUBLICATIONS

Paper 1. Kverneland M, Tauboll E, Selmer KK, Iversen PO, Nakken KO. Modified Atkins diet may reduce serum concentrations of antiepileptic drugs. *Acta Neurol Scand* 2015; **131**(3): 187-90.

Paper 2. Kverneland M, Selmer KK, Nakken KO, Iversen PO, Tauboll E. A prospective study of the modified Atkins diet for adults with idiopathic generalized epilepsy. *Epilepsy Behav* 2015; **53**: 197-201.

Paper 3. Kverneland M, Molteberg E, Iversen PO, Veierød MB, Taubøll E, Selmer KK, Nakken KO. Effect of modified Atkins diet in adults with drug-resistant focal epilepsy: A randomized clinical trial. Epilepsia 2018; **59(8)**: 1567-1576.

Paper 4. Kverneland M, Taubøll E, Molteberg E, Veierød MB, Selmer KK, Nakken KO, Iversen PO. Pharmacokinetic interaction between modified Atkins diet and antiepileptic drugs in adults. Submitted

ABBREVIATIONS

AED	antiepileptic drug
ATP	adenosine triphosphate
CKD	classical ketogenic diet
GABA	gamma amino butyric acid
KDT	ketogenic diet treatment
LGIT	low-glycaemic-index treatment
MCT	medium chain triglyceride
MKD	modified ketogenic (Atkins) diet
NCE	National Centre for Epilepsy
PPARα	peroxisome proliferator-activated receptor alpha
RCT	randomised controlled trial

CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1. Background

In Norway there is one national hospital for patients suffering from severe epilepsy, the National Centre for Epilepsy (NCE). These patients have often suffered from debilitating and frequent epileptic seizures for many years, and most of them have tried several antiepileptic drugs (AEDs) without achieving seizure control. Epilepsy surgery may have been evaluated and found unsuitable or attempted unsuccessfully. For this vulnerable and heavy-burdened patient group, life expectancy is shortened and psychiatric comorbidities are frequent. Their quality of life is often reduced, and many have not been able to complete education, enter working life or establish a family. To improve their lives, professionals are constantly searching for new treatment options.

During the last 2-3 decades, ketogenic diet treatment (KDT) has turned out to be an alternative or additional therapy to drugs and surgery for these patients. After the diet had been proven successful among children with severe epilepsy, KDT was included in the treatment options for children admitted to NCE from the late 1990s (1).

In 2010, when we started planning our project, studies of the effect of dietary treatment in adults with drug-resistant epilepsy were mostly lacking. Only a handful of small, prospective studies had been published (Table 1A).

We were aiming at finding out whether KDT could be as beneficial in adults with severe epilepsy as in children. We saw an opportunity to study the effect of such treatment in adults as this was hitherto an almost unexplored area of research. Moreover, we

concluded that many patients referred to the NCE were suitable for trying such a treatment option.

However, there were some practical issues to be solved at the NCE. Among the neurologists and the nursing staff at the wards for adults, the knowledge and experience with dietary treatment were sparse. Also, there was no place to educate and prepare meals to the patients. These issues were gradually solved, and we then decided to perform a randomised controlled trial (RCT) to study the efficacy and tolerability of a variant of KDT, namely modified ketogenic (Atkins) diet (MKD) in adults with drug-resistant epilepsy.

In order to conclude on whether the diet was effective or not, statistical calculations showed that 92 participants ought to be included and randomised to either diet or control group. We chose to include only people with focal epilepsy, since this group is the largest and the most difficult-to-treat in the adult population. In March 2011, we included and randomised the first participants.

Unexpectedly, early in the course of the project we observed that patients starting the dietary treatment had a reduction of the serum concentrations of the AEDs. This phenomenon had not been described earlier, and we published a thorough description of four cases (Paper 1). We realized that such a reduction of the serum concentration of AEDs might negatively influence our primary outcome measure in the RCT, i.e. the seizure frequency.

In addition to the patients with focal epilepsy, we prospectively tried the MKD in 13 patients with drug-resistant generalised epilepsy, using the same protocol. However, these participants were not randomised. The results were published in Paper 2.

Inclusion of participants in the RCT went slower than anticipated. Thus, in 2017 we decided to end the inclusion of patients after having included 75 participants with drug-resistant focal epilepsy (Paper 3). We found a significant reduction in seizure frequency in the diet group compared to the controls among those who completed the intervention. However, the effect was moderate, with 10 of 24 patients (42%) in the diet group achieving 25% or more seizure reduction. AED serum concentrations were reduced during the dietary treatment (Paper 4).

Today, for adults with drug-resistant epilepsy, dietary treatment is an established treatment option at the NCE. About 20 patients start dietary treatment annually, and about 70 adults using the diet have currently a long-term follow-up at the centre.

Since we started this project, the low-carbohydrate diet has become a popular diet to achieve weight loss in Norway. This trend was advantageous for us because more suitable food products became available. On the other hand, claims were made in newspapers and other media that such a diet would increase risk of vascular disease, and some of our patients became worried. However, independent of the diet being a trend diet or not, we advise our patients to choose a healthier diet by using less animal derived saturated fat and more nuts, seeds, plant oils and vegetables. We recommend a diet that is as close as possible to the diet recommended by the Norwegian Health Authorities. Also, the patients' lipid profile is carefully examined and evaluated.

1.2. What is epilepsy?

Epilepsy is a disease with many causes. The common denominator is recurrent unprovoked epileptic seizures due to abnormal electrical discharges in the brain. Causes are categorised as genetic, structural, metabolic, infectious, immunological, and

unknown (2). Being one of the most common neurological diseases, the prevalence is estimated to be 0.6 -0.7% (3). In spite of the fact that there are currently 25 – 30 different AEDs on the Norwegian market, about 30% of the patients do not achieve adequate seizure control, and hence about 12 000 persons live with drug-resistant epilepsy in Norway (4).

The occurrence of epilepsy is even higher in low-income than in high-income countries (5). Recurrent unpredictable seizures are often accompanied by insecurity, social stigma, reduced work capacity and poor quality of life. Impaired memory and ability to concentrate and psychiatric comorbidities are also common (6). Moreover, there is a considerable increased risk of seizure-related injuries and premature death in this sub-population (7). The occurrence of sudden and unexpected death is 2 – 3 times as high as for the general population. With seizure onset in childhood, the ratio is 6.4 – 7.5 compared to people without epilepsy, and when comparing those with drug-resistant epilepsy to those who are seizure free, the relative risk of premature death is estimated to 9.3 - 13.4 (7).

1.2.1 Definition and classification

In 2005 epilepsy was defined by the International League Against Epilepsy and the International Bureau for Epilepsy as:

A disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure (8).

Whether having one single unprovoked seizure was sufficient for diagnosing epilepsy, was discussed in the following years. Then, in 2014 this definition was further elaborated, and to diagnose epilepsy it was decided that one out of the three following criteria had to be fulfilled (9):

- the occurrence of at least two unprovoked seizures or
- having had one unprovoked seizure and a likelihood of more than 60% of having another seizure
- the seizure is part of a known epilepsy syndrome

In 2017, the International League Against Epilepsy updated the classification of epileptic seizures and epilepsy (2, 5). According to this classification, clinicians should determine the patient's seizure type, epilepsy type, and if appropriate, epilepsy syndrome.

Seizure types are classified according to localization of seizure onset; either a) generalised (arising in both hemispheres) or b) focal (arising focally in one hemisphere) or c) unknown (10). Generalised seizures are subdivided into motor or non-motor with several subtypes in each group. Focal seizures are grouped according to awareness (intact or impaired), and with sub-classification in motor or non-motor, and with or without developing into tonic-clonic seizures. Specific seizure characteristics are added as appropriate, for example autonomic, behaviour arrest, cognitive, emotional or sensory symptoms (10).

Epilepsy types are classified into four classes according to localization of seizure onset (2, 5, 10): 1) generalised (arising from the whole brain at once), 2) focal (originates in one focus in one hemisphere), 3) combined generalised and focal (examples are Dravet

syndrome and Lennox Gastaut syndrome) or 4) epilepsies of unknown localization of onset. Focal epilepsies include also multifocal disorders.

The third level of classification is to diagnose an ***epilepsy syndrome.*** Especially in childhood there are several well-defined syndromes which are important to recognise as it determines the diagnostic work-up, treatment, prognosis and counselling.

1.2.2 Epilepsy in childhood vs adulthood

Epilepsy in adulthood differs somewhat from epilepsy in childhood as the immature brain of children has a greater propensity to generalised electrical discharges than the adult brain. Thus, in children generalised epilepsies are more frequently seen than in adults. While the distribution of generalised and focal epilepsies is about 50/50 among children, in adults this is about 20/80 (11).

1.2.3 Epilepsy treatment options

Drugs are the mainstay of epilepsy treatment (5). There is no single drug preferred to all patients, rather, which drug to try first is considered on the basis of epilepsy aetiology, seizure type(s), epilepsy syndrome, comorbidity, age, body weight, and sex (12). About 50% becomes seizure free with the first AED tried (13). Another 10 – 12% respond to the second drug, while scarcely 5% respond to a third or fourth attempted drug. If seizures persist after treatment attempts with two adequate, well tolerated AEDs, the epilepsy is termed *drug-resistant* (4). The term drug-resistant is used interchangeably with medically refractory, medically intractable and pharmaco-resistant.

AEDs are broadly categorized according to when they became available on the market; those released in the period from 1912 to the 1990s are first generation drugs, while the ones released later are second and third generation drugs. Despite more than 15 drugs

have been launched after 1990, the number of drug-resistant patients have not been reduced. However, adverse effects and pharmacokinetic interactions appear to be fewer and less severe with the newer drugs (12).

Benzodiazepines are regularly used as seizure stopping treatment in cases of seizure clusters or status epilepticus.

1.2.4 Non-pharmacological treatments of epilepsy

In patients with severe focal epilepsy, if two AEDs have failed, resective surgery may be an option. These patients should be admitted to a tertiary epilepsy centre without delay. Surgery is the only treatment that may remove the epileptic focus and has a potential of curing the disease. Good outcome depends on a proper pre-surgical work-up, type of epilepsy and the localisation of the epileptogenic area. Adequate post-operative follow-up is also of importance for the long-term outcome (12).

Vagus nerve stimulation is another treatment option in drug-resistant epilepsy where surgery is not suitable. It is sometimes called a "pacemaker of the brain". The device is implanted in the chest, and a wire from the device is twirled around the left vagus nerve and sends electric pulses to central areas of the brain at regular intervals in order to counteract seizure generation (5).

Beside AEDs, respective surgery and vagus nerve stimulation, KDT is a fourth treatment option for patients with severe epilepsy. This will be the topic of the rest of this thesis.

1.3. Dietary treatments of epilepsy

From ancient times, it has been known that fasting could reduce the frequency of epileptic seizures. In the beginning of the 20th century, Dr Hugh Conklin confirmed that

fasting had a seizure-reducing effect, and a few years later Dr Russel Wilder found that a high fat and low carbohydrate diet had a similar effect by imitating the metabolic responses to fasting (14). The diet, later named "classical ketogenic diet" (CKD) was found efficient in treating epilepsy, both in children and adults (15, 16).

In 1930, results from the first prospective trial of CKD in adults with epilepsy were published. Barborka et al. reported that after twelve months of treatment, 12% of the patients became seizure free, 44% benefited with reduced seizure frequency and less severe seizures, while 44% did not benefit at all (16). Of these, 9% experienced a seizure aggravation. However, the results of this study are difficult to compare to studies carried out today as the drugs available in 1930 were modest, and the participants in Barborka's study might therefore not have been drug-resistant according to the current definition.

The only AEDs available at that time were phenobarbital and bromides. After 1938, when phenytoin was launched, drugs were preferred to the laborious diet, and the CKD was more or less forgotten in the years to come.

However, at Johns Hopkins Hospital in the USA, for more than 40 years, a few children were treated with CKD annually under supervision of dietitian Millicent Kelly (17). Also Dr John Freeman was a long term advocate for the dietary treatment. In these early days of dietary treatment, fasting initiation, fluid restriction and calorie restriction was practiced, believing that this would improve efficacy.

In 1993, Hollywood film producer Jim Abrahams founded the Charlie's Foundation to promote the diet after his son Charlie had become seizure free on the CKD. In 1997, Charlie's father directed the movie "First Do No Harm" starring the actress Meryl Streep, which resulted in a great breakthrough and a renaissance for the CKD. Since then, both

dedicated professionals and patients' organizations in the USA and the UK have spent immense efforts to promote the diet, which is now used all over the world (18).

In 1971 another variant of KDT was introduced by Dr Huttenlocher; the Medium Chain Triglyceride (MCT) diet (19).

An important milestone was reached in 2008 when Neal et al. published the results of the first RCT on dietary treatment. They randomised 145 children with drug-resistant epilepsy to either CKD in addition to current AED treatment or to no change in treatment (Table 2) (20). This well conducted London-based study proved that the CKD could be an effective treatment for children with difficult-to-treat epilepsy. Thus, the Neal-study became a breakthrough for dietary treatment for children with severe epilepsy.

In 2011, when we started our project, it was not clear whether the dietary treatment could be of benefit also to *adults* with drug-resistant epilepsy. Many neurologists were sceptical to such a treatment. They argued that the diet would be too difficult to implement and adhere to among adult patients. At that time, results from four smaller prospective trials in adults had been published (Table 1A) (21-25). The studies showed a highly variable seizure reducing effect of the diet, with 13-52% achieving >50% seizure reduction. There was a high drop-out rate, but MKD seemed slightly easier to adhere to than CKD.

Beside effects on the seizure susceptibility, there were reports of favourable effects of the diet on cognition, well-being and quality of life. Of the reported side effects were gastrointestinal symptoms (nausea, vomiting, diarrhoea, constipation), weight loss, elevation of low density lipoproteins and triglycerides, and menstrual irregularities.

Table 1A. Prospective studies in adults with drug-resistant epilepsy published between 1990 and 2010, comparing seizure frequency under dietary treatment to baseline seizure frequency.

First author	Country	Publ year	Diet type	n	Age (years)	Seizure reducing effect
Sirven (21)	US	1999	CKD Ratio 4:1 with fluid restriction	11	19-45	After 8 months: 3 (27%) achieved >90% seizure reduction and another 3 (27%) achieved >50% seizure reduction; 4 discontinued
Kossoff (23)	US	2008	MAD 15-20 g carbo-hydrate	30	18-53	At 3 months: 14 (47%) achieved >50% seizure reduction; 10 discontinued At 6 months: 10 (33%) achieved >50% seizure reduction; 16 discontinued
Carrette (22)	Belgium	2008	MAD 20 g carbo-hydrate	8	30-54	After 6 months: 1 (13%) achieved >50% seizure reduction, 2 (26%) achieved 25-50% seizure reduction; 1 did not start; 5 discontinued
Mosek (24)	Israel	2009	CKD ratio 3:1	9	23-36	At 3 months: 2 (22%) achieved >50% seizure reduction; 1 did not start; 6 discontinued

Table 1B. Prospective studies in adults with drug-resistant epilepsy published from 2010 until present, comparing seizure frequency under dietary treatment to baseline seizure frequency.

First author	Country	Publ year	Diet type	n	Age	Seizure reducing effect
Klein (25)	US	2010	CKD ratio 3:1	12	24-65	At 4 months: 2 (17%) achieved >90% seizure reduction; 3 (25%) achieved >50% seizure reduction; 5 (42%) achieved >25% seizure reduction; 1 worsened; 1 discontinued
Smith (26)	Canada	2011	MAD 20 g carbo-hydrate	18	18-55	After 3 months: 2/17 (12%) achieved >50% seizure reduction; after 6 months: 4/14 (28%) had >50% seizure reduction, and after 12 months: 3/14 (21%) experienced >50% seizure reduction; 4 discontinued before 12 months
Lambrechts (27)	The Nether-lands	2012	CKD/ MCT combined	15	20-40	After 4 month: 1/9 (11%) experienced >50% seizure reduction After 12 months 2/5 (40%) had >50% and 3/5 (60%) achieved <50% seizure reduction. 10 discontinued at 12 months
Cervenka (28)	US	2012	MAD 20 g carbo-hydrate	22	18-66	Email follow-up, no hospital visits or admission After 3 months: one was seizure free (5%), 3 (14%) had > 90% seizure reduction and another 2 (9%) experienced > 50% seizure reduction; 8 discontinued
Nei (29) [a]	US	2014	CKD Ratio 4:1	29	11-59	After 3-9 months: 15 (52%) had > 50% seizure reduction. 2 not started; 9 had no effect; 3 had seizure increase
Schoeler (30)	UK	2014	CKD 5/23 MAD 18/23	23	16-65	After 12 months or more: 9 (39%) achieved >50% seizure reduction; of these 7 followed MAD and 2 were on CKD
Kverneland (31)	Norway	2015	MAD	13	16-57	After 3 months: 4 (31%) had >50% seizure reduction; 7 discontinued, 1 due to prominent seizure increase
Cervenka (32)	US	2016	MAD	106 [b]	18-70	At 3 months: 17 (16%) were seizure free; 38 (36%) achieved ≥50% seizure reduction; 15 (14%) experienced <50 seizure reduction; 6 (6%) became worse or had no change; 25 (23%) discontinued

[a] Some participants are also covered in the publication by Sirven 1999

[b] Of whom 84 had drug-resistant epilepsy.

Table 2. Open label randomised clinical trials performed to compare seizure frequency on dietary treatment to care as usual

First author	Country	Publ year	Diet type	n	Age (years)	Seizure reducing effect
Neal (20)	UK	2008	CKD	145	2–16	7% (diet) vs 0% (control) had > 90% seizure reduction, p=0.0582 38% (diet) vs 6% (control) had >50% seizure reduction, p<0.0001
Neal (33)	UK	2009	MCT vs CKD	145	2-16	7% (CKD) vs 3% (MCT) had > 90% seizure reduction, p=0.442 25% (CKD) vs 29% (MCT) had >50% seizure reduction, p=0.578
Sharma (34)	India	2013	MKD	102	2-14	30% (diet) vs. 7.7% (control) had >90% seizure reduction, p=0.005 52% (diet) vs 11.5% (control) had >50% seizure reduction, p<0.001
Lambrechts (35)	The Nether-lands	2016	CKD	57	1-18	50% (diet) vs. 18% (control) had >50% seizure reduction, p=0.024[a]
Zare (36)	Iran	2017	MKD	66	18-57	35% (diet) vs 0 (control) had >50% seizure reduction, p=0.001
Kverneland (37)	Norway	2018	MKD	75	16-65	13% (diet) vs 6% (control) had >50% seizure reduction, p=0.65 42% (diet) vs 16% (control) had >25% seizure reduction, p=0.03

[a]Comparing change of mean seizure frequency in both groups

1.3.1 Several variants of the diet

Today, several variants of KDT are in clinical use. The diet variants are slightly different in the way they are practiced with respect to meal frequency and how the calculations of meals are carried out. A brief overview is given in Table 3. The concept of a *ketogenic ratio* is a way of calculating the relationship between the macro-nutrients fat, protein and carbohydrate in meals and recipes, and can be used to evaluate individual food records and compare diet variants. The definition of ketogenic ratio most commonly used worldwide is fat / protein + carbohydrate, measured in grams. This implies that the more fat and less protein and carbohydrate, the higher ketogenic ratio. The ketogenic ratio can be compared to the dosage of drugs; increasing the ketogenic ratio is a way to increase the strength of the dietary treatment.

The early variant of the ketogenic diet is nowadays often denoted "the classical ketogenic diet" (CKD). It is mostly used in children and those fed via gastrostomy. Up to recently, fasting initiation, fluid and caloric restriction were practiced, all assumed to optimize the effect of the diet. In 2005, a RCT showed that fasting initiation of CKD did not give a better efficacy than a gradual initiation (38). Fluid restriction is presumed to increase the risk of kidney stones and is now abandoned. Calorie restriction, shown to have an independent seizure reducing effect in mice (39), was traditionally used for children on the CKD, limiting energy to 80-90% of the recommended amount. It has, however, not been found to have additional seizure reducing effect and is no longer in use (40).

Table 3 Brief overview of the variants of the ketogenic diet

1. Classical ketogenic diet (CKD)
Up to 90% of the energy comes from fat, and ketogenic ratios are 2:1 – 4:1. Meals are served at regular hours calculated to provide exactly the same amount of energy, fat, protein and carbohydrate. The diet is used for children with drug-resistant epilepsy and patients with gastrostomy.
2. Medium Chain Triglyceride (MCT) diet
The MCT-diet resembles the classic ketogenic diet, but 30 – 60% of the fat is replaced by Medium Chain Triglyceride (MCT) oil. MCT oil provides more ketones than oil consisting of long chain fatty acids. This allows for more carbohydrate and a larger variety of foods.
3. Modified ketogenic (Atkins) diet (MKD)
Free amounts of food and drink, no fixed meal schedule. The daily amount of carbohydrate is limited to 10 – 30 grams per day and high intake of fat is encouraged. The diet is used for older children, adolescents and adults. Ketogenic ratio may range from 1:1 to 3:1, depending on total energy intake and intake of fat versus protein.
4. Low-glycaemic-index treatment (LGIT)
The diet is similar to the MKD, but the intake of carbohydrate is limited to 40 – 60 grams per day, including fibres, and the foods containing carbohydrate must have a glycaemic index[a] of < 50.

[a] Glycaemic index is defined as the extent of blood glucose increase 2 hours after the consumption of an amount of this food item containing 50 g carbohydrate (41).

The diet used in our project, MKD, is more common among adults, and got its name from Robert Atkins who introduced a low-carbohydrate diet as part of a weight loss programme. To distinguish the diet used against epilepsy from the weight reduction diet, some denote this diet the modified ketogenic diet, but in scientific literature, the Atkins name is well established. We therefore name the treatment we have employed the modified ketogenic (Atkins) diet, with the acronym MKD.

The first mention of a modified ketogenic diet in scientific literature that we are aware of was in 1998 (42). In the UK, the term modified ketogenic diet is frequently used instead of modified Atkins diet, and some suggest that modified ketogenic diet in UK is practiced with higher amount of fat than in the US' modified Atkins diet (43). However, there seems to be no important difference between the two variants according to a more recent survey (44). In a recent practice paper from the American Academy of Nutrition and Dietetics, the term modified ketogenic diet was used to group modified Atkins diet and low-glycaemic-index treatment (LGIT) (45). Thus, the term modified ketogenic diet seems to have different meanings in the US and the UK. A fourth diet variant is the LGIT (46).

Figure 1 shows the distribution of protein, fat, and carbohydrate in the four mentioned diet variants compared to the diet recommended by the Norwegian Health Authorities.

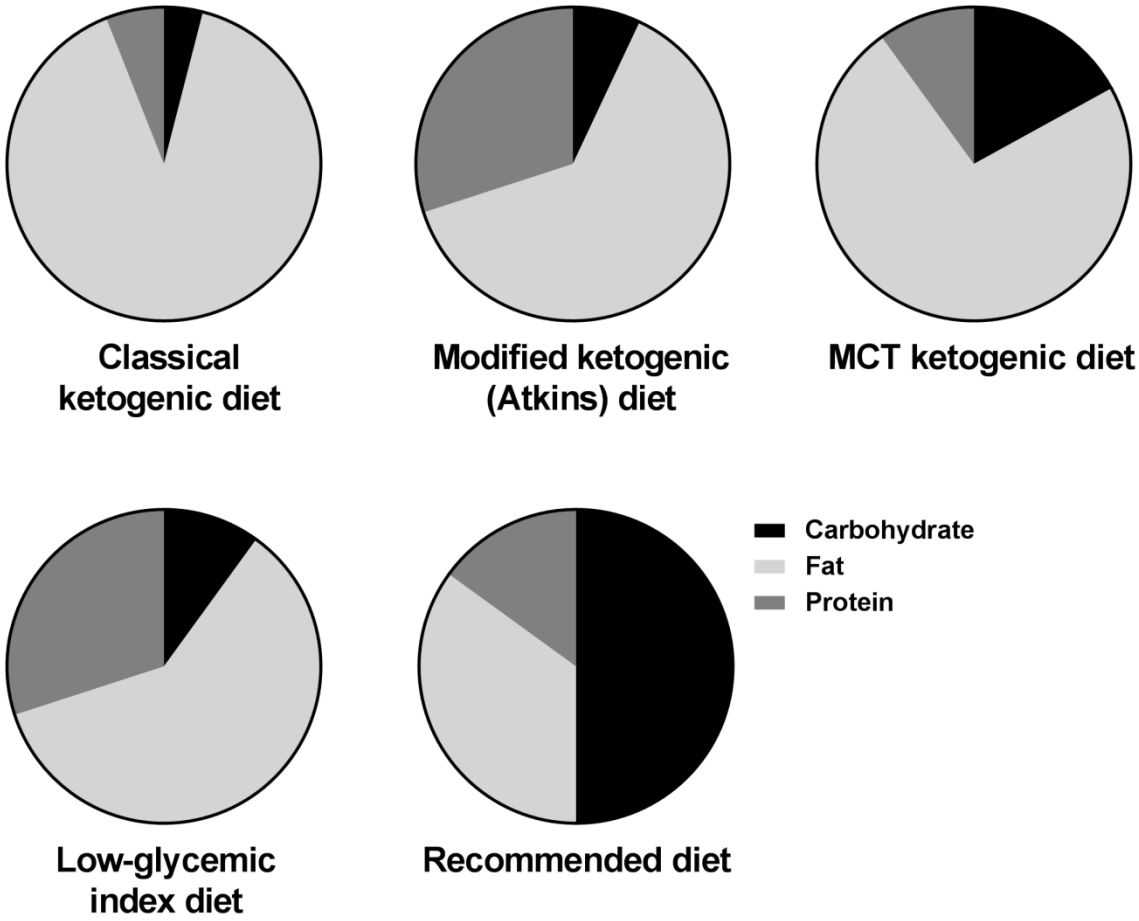


Figure 1 Macro-nutrient distribution in the most common variants of the ketogenic diet and the Norwegian recommended diet.

1.3.2 Effect of dietary treatments in epilepsy

There is currently no doubt that dietary treatment has a place in treating severe childhood epilepsy. Also, among adults these treatments are used at increasing rates. However, to date only five RCTs comparing KDTs to conventional treatments have been published; three in children and two in adults with drug-resistant epilepsy (Table 2). As already mentioned, the RCT by Neal and co-workers from 2008 became a breakthrough for the dietary treatment in children (20). The same group showed that MCT diet is

equally effective as the CKD (33). Furthermore, since 2008 the number of publications on dietary treatment has increased exponentially, but to date only another two RCTs comparing the effect of the diet to standard treatments in children have been published (Table 2) (34, 35).

Currently, only two RCTs on dietary treatment in adults with severe epilepsy have been completed (36, 37). The first study was performed in Iran. However, the study design was questionable (36). We performed the second RCT, published in 2018 (37).

A list of all prospective studies on adults carried out is given in Tables 1A and 1B, showing the wide variation in results. According to two reviews published in 2014/2015 summarizing dietary treatment in adults, the MKD offers the patients a mean seizure reduction of 30 – 34% (47, 48).

1.3.3 Predictors of effect of the diet

To date, predictors of effect of the diet are largely unknown.

Age

Although results are conflicting, age may be a factor; the younger age, the higher likelihood of success. Children in general seem to have a better seizure-reducing effect than adults. Freeman et al. concluded that children younger than 8 years of age had a higher likelihood of achieving more than 50% seizure reduction compared to older patients (1). Also, although not significant, Maydell and co-workers found a similar trend: "a greater than 50% seizure reduction may be less frequent in subjects older than 12 years than in younger age groups" (49).

However, in a prospective study of 56 children and adults aged 1-23 years there was no correlation between efficacy and age (50). Furthermore, in 2003 Mady et al. published a retrospective analysis of 45 patients, aged 12–19 years (51). They found no correlation between efficacy and age. Barborka, studying adults, stated that "older patients are the least likely to be benefitted" (16).

Duration of disease and age of onset

It has been hypothesized that untreated seizures may cause mitochondrial injury, which in turn results in even more treatment resistant epilepsy (52). Thus, the rate of success with the diet may depend on the duration the person has lived with poorly controlled seizures. On the other hand, low age of seizure onset may indicate a severe underlying disease and thus poorer response to treatment.

Besides, there are physiological differences between children and adults with higher plasticity in the paediatric brain. Among 23 children with infantile spasms, a better outcome was observed in those younger than 1 year and previous exposure to three or fewer AEDs when dietary treatment was started, compared to those who started such treatment later on (53). In 2010 the same group published results of dietary treatment in 104 infants with infantile spasms. This study showed no correlations between age of diet onset and efficacy, but those with spasm onset at 0.5 years had better effect than those with spasm onset at 0.4 years (54).

In general, it seems that children with epilepsy onset before one year of age respond poorer to dietary treatment than those with later seizure onset, probably because of more severe underlying epilepsy aetiology (55).

Biochemical predictors

In searching for biochemical predictors of effect, blood samples were drawn from 215 children and 13 adults before and after three months of dietary treatment (56). Interestingly, baseline acetyl carnitine was found to be significantly higher in those who responded to the diet compared to those who did not. Also, there was a trend for free carnitine and other acyl carnitine esters to be higher in responders versus non-responders. It has been speculated that low free carnitine may reduce efficacy of KDT due to reduced efficacy to transport fatty acids into the mitochondria for beta-oxidation (57).

Genetic factors

The variable efficacy of the dietary treatment raises the question if genetic factors may have an impact on the effect of the diet (58). This is obviously the case for the two genetic disorders; Glucose transporter protein 1 deficiency syndrome and Pyruvate dehydrogenase deficiency where the diet compensates a metabolic dysfunction (59, 60). This may also be the case for other epilepsy syndromes that respond to the dietary treatment, but where the genetic failure is still not known.

Other gene variants could play a role for the individual response to the diet. Schoeler and co-workers analysed the relationship between response to dietary treatment and variants of two genes (*KCNJ11* and *BAD*) among 303 patients without finding any correlation among those with minor allele frequency < 0.01 (61). However, the sample size was too small to detect relationships between rare gene variants. Of great interest was a genome-wide association study of responders versus non-responders published in 2018 (62). Here, *CDYL*, a gene that has been associated with epilepsy susceptibility in mice, appeared as a possible candidate gene for an association.

There are some data in support of a better effect of the diet in children with genetic versus non-genetic epilepsies and in generalised versus focal epilepsies (63, 64). However, at the current stage there is not enough evidence to draw firm conclusions in this respect.

1.3.4 Does CKD show better efficacy than the MKD?

Whether there is a relationship between the higher fat intake and lower carbohydrate intake, i.e. the higher ketosis, the better effect of the diet is unclear. In animal studies, Bough et al. found a correlation between rats that developed high levels of ketosis showing high threshold for seizure induction (65). However, Likhodii et al. concluded

that the seizure reducing effect of ketogenic diet in rats did not improve with increasing levels of ketones (66).

Among children <2 years of age, no difference in response was observed between ketogenic ratios of 2.5:1 and 4:1 in a randomised controlled trial (67). Also in MKD, no difference regarding efficacy has been found in patients using either 10 or 20 grams of carbohydrate in the diet (68).

However, Kossoff and co-workers tried CKD in a group of children who had failed MKD and found that some responded to CKD, possibly due to higher ketogenic ratio and stricter diet administration (69). In a cohort of 63 children, Agrawal et al. found better response in those with high ketogenic ratio (55). Interestingly, in a RCT from South Korea, comparing treatment with CKD versus MKD in children aged 1-18 years, no statistically significant difference in response was found between the two diet variants (70). However, in the group of children aged 1–2 years, after 3 months the rate of seizure freedom was significantly higher among those treated with CKD than among those treated with MKD (53% on CKD vs 20% on MKD, p = 0.047). Miranda and co-workers compared the effect of MKD to CKD in a Danish cohort. They found a trend towards higher efficacy among the children on CKD (p=0.06), but when adjusting for age (the age of the patients on MKD was higher than those on CKD), this trend disappeared (71).

Despite the current data on this topic is conflicting, the results suggest that for some patients, perhaps particularly among the younger age groups, the ketogenic ratio may be of importance for the efficacy of the diet.

1.3.5 Interaction between diet and drugs

The metabolism of most AEDs takes place in the liver. Exceptions are gabapentin, lacosamide, levetiracetam, pregabalin and vigabatrin which are mainly metabolised in kidneys (72).

When combining CKD and phenobarbital, serum concentrations of phenobarbital has in some children increased considerably (73), and drug intoxication has been feared. However, other reports could not confirm this (74), and for valproate serum concentrations may even be reduced (75, 76).

Several reports have suggested that some drugs may be more favourable than others in combination with KDT, but the evidence is poor and no conclusions can be made. In 115 children treated with CKD in Johns Hopkins Hospital, children receiving phenobarbital were significantly less likely to have a >50% seizure reduction than those using zonisamide (p=0.003) (77). In a Dutch paediatric study, children using concomitant lamotrigine seemed to have less effect of the CKD than those using other AEDs (78).

The combination of valproate and KDT may be a beneficial treatment combination, but valproate may also increase risk of pancreatitis and other serious side effects (79). In a study of 75 children treated with a combination of CKD and valproate, two children who withdrew valproate experienced hyper-ketosis after drug withdrawal (80). The problem resolved after the ketogenic ratio of the diet was reduced.

1.3.6 Absolute and relative contraindications of the diet

A pre-diet evaluation of all factors that may contraindicate KDT is essential. A list of disorders that are absolute contraindications to use of KDT can be found in the 2018 optimal treatment consensus document (81). In children, a screening for metabolic

defects is mandatory. In adults, however, this is not necessary because such severe metabolic disorders are normally discovered during childhood. Hence, metabolic testing in adults is performed only on indication, not as a routine. Adults may have developed diseases that may contraindicate dietary treatment. Vascular disease is one example.

Many adults with drug-resistant epilepsy experience poor memory and reduced cognitive functioning. This entails challenges in cooking and adhering to the diet, and must be taken into account in the pre-diet evaluation.

1.3.7 Dietary treatment of rare syndromes

In Glucose transporter protein-1 deficiency syndrome and Pyruvate dehydrogenase deficiency KDT is the main treatment. Furthermore, a comprehensive list has been made of rare syndromes and conditions that may respond better to diet than to drugs. Examples are Angelman syndrome, Complex 1 mitochondrial disorders, Dravet syndrome, epilepsy with myoclonic–atonic seizures (Doose syndrome), Febrile infection-related epilepsy syndrome (FIRES), Infantile spasms, Ohtahara syndrome, super-refractory status epilepticus, Tuberous sclerosis complex. Also, formula-fed (solely) children or infants may be considered for KDT. The list can be found in the "Updated recommendations of the International Ketogenic Diet Study Group published in 2018" (81).

Due to various reasons, many of these conditions are not found among the adults. However, Glucose transporter protein 1 deficiency syndrome, Pyruvate dehydrogenase deficiency, Angelman syndrome, Dravet syndrome, Doose syndrome (myoclonic-atonic

epilepsy), Tuberous sclerosis complex and super-refractory status epilepticus are all disorders where KDT may be relevant also for adults.

Other diagnoses associated with difficult-to-treat seizures among adults, and where KDT has been reported to be beneficial in some cases, are cortical malformations, Lennox-Gastaut syndrome, Rett syndrome, juvenile myoclonic epilepsy, Lafora body disease and childhood absence epilepsy (81).

At the NCE, children and adults diagnosed with Glucose transporter protein 1 deficiency syndrome and Pyruvate dehydrogenase deficiency are currently recommended treatment with CKD or MKD.

1.3.8 Effects of the diet beyond seizures

According to many patients, parents and caretakers, and confirmed in some research papers, the diet may improve on not only seizure susceptibility, but also seizure duration and severity and cognitive functioning (20, 21, 25, 27, 30). Also improved sleep has been reported in children (82). According to our clinical experience, such effects may be important motivators to continue the diet. In 2018, a systematic review article confirmed a positive effect of the diet on cognition, based on the results of both subjective and objective methods (83). Van Berkel et al. suggested that cognitive improvements were due to both reduced seizure frequency and to an independent effect from the KD (83).

During the last 20 years, a few studies have addressed the behavioural effects of the dietary treatment in children, using validated neuropsychological methods (84-86). In

an assessment of adults using the KDT, Lambrechts et al. found a considerable improvement in mood and quality of life, but no change in global cognitive performance (27).

However, the findings from these studies are varied, possibly due to the great heterogeneity among the studied patients regarding age, developmental stage, cognitive and neuro-behavioural comorbidities. Hopefully, more research on this topic will give us more valid information on the effects of the diet beyond seizures, both in short and long term. Recently, an interesting way of assessing quality of life in parents with children on KDT has been launched (87).

1.3.9 KDT in super-refractory status epilepticus

Status epilepticus is a severe condition with ongoing seizures not responding to seizure stopping drugs. Super refractory status epilepticus (SRSE) is defined as continuous or recurrent seizures without normalization of consciousness lasting for 24 h or more despite administration of an intravenous anesthetic (midazolam, propofol, ketamine, or barbiturate), or recurrence of status epilepticus on weaning of intravenous anesthetics (88).

KDT was suggested as an effective treatment to resolve status epilepticus in adults, but a publication bias was suspected (47, 89). A prospective study from 2017 indicated that CKD may be effective in treating adults with super-refractory status epilepticus (90).

1.3.10 Ketogenic diet as epilepsy treatment in pregnancy

KDT is generally not recommended in pregnancy. Ketosis is related to starvation and can be critical for development of the foetus. From the Dutch famine in 1944-45 it has been

thoroughly documented that starvation in periods of pregnancy may predispose for impaired health of the child in adulthood (91). Mouse studies report reduced maternal fertility and considerable deviation in brain structure of ketogenic dams compared to standard diet dams (92). Ketones cross the placenta and reach the same concentration in the foetus as in the mother (93). Nevertheless, the first case series reporting two successful pregnancies in women using KDT was published in 2017 (94).

1.3.11 How long should the treatment last?

In most cases, after having used the diet in 2-3 months it is possible to decide whether a seizure-reducing effect has been achieved or not. For children with >50% seizure reduction (often termed responders), the recommended length of treatment is two years (81). Some children may retain the seizure reducing effect even after gradually have tapered the diet over some months (95). However, for most patients using dietary treatments, the effects do not outlast the treatment. Some responders may use the diet for several years, sometimes the whole life, and in these patients side-effects should be monitored on a regular basis.

1.4. Side-effects of dietary treatments

Although KDT is generally well tolerated, several side-effects are reported and appear to be similar in adults and children (96). Many early-onset side-effects are mild, transient or can easily be resolved in most patients (81). It is presumed that the higher ketogenic ratio, the more side-effects (97). From clinical experience we anticipate that vulnerability to longer-term side-effects may vary with age, severity of disease, epilepsy

syndrome, comorbidities and predisposition. Side-effects that may develop during long-term KDT need to be evaluated and preferably prevented.

During the first weeks, transient hypoglycaemia, tiredness and lack of energy is common, but resolve as the metabolism adapts to the new source of energy.

1.4.1 Diet induced acidosis

Metabolic acidosis arises from lowered pH in the blood caused by elevated levels of ketone bodies; the higher numbers of ketones, the higher risk of acidosis. The acidosis is normally mild and asymptomatic (81), but is thought to be responsible for side-effects such as kidney stones, impaired bone health and even growth retardation in children (98-100). Also, it has been proposed to cause gastrointestinal disturbances, such as nausea, vomiting, diarrhoea and constipation by acidification and inactivation of pancreatic digestive proenzymes and zymogens (98).

In combination with drugs such as acetazolamide, topiramate or zonisamide, the metabolic acidosis may be aggravated since these AEDs inhibit carbonic anhydrase, an enzyme that maintains acid-base balance (101).

1.4.2 Gastrointestinal disturbances

The most common side effects in both children and adults on all KDT variants are gastrointestinal disturbances, such as nausea, vomiting, diarrhoea, exacerbation of gastroesophageal reflux, flatulence, abdominal pain and constipation (20, 47, 102-104). According to Neal et al, about a quarter of the 55 participants on CKD reported such problems during three months (20). Similar rates are confirmed by others (102). Such

side-effects are, however, mostly managed by dietary adjustments or medication and are not normally the reason for early termination of the treatment (20, 81).

1.4.3 Weight change

Ketosis is suggested to suppress the increase in appetite that arises when using a calorie restricted diet (105). Nowadays, with non-fasting initiation protocols and no calorie restriction, weight loss among children on CKD is less common (35, 38, 67). However, among adults using MKD, weight loss is frequently reported, mostly as an advantageous side-effect (22, 23, 30, 31, 37, 57). It may, however, become a problem among patients with poor appetite and/or in those using topiramate, a drug associated with weight loss (106). From our clinical practice we have experienced that weight increase can be a problem when MKD is combined with valproate.

1.4.4 Lipid profile and risk of atherosclerosis

Among children using KDT for six months, elevation of very low-density lipoprotein, low-density lipoprotein, high-density lipoprotein, and non-high-density lipoprotein cholesterol, triglycerides, total apolipoprotein B, and apolipoprotein A-I has been reported (107). In this report, however, there was no description of fat type used in the diet, but presumably there was a high percentage of saturated fat. Studies in adults on MKD report similar findings, although not as striking (37, 47). However, among 20 adults using MKD for one year, McDonald and co-workers found significantly higher levels of

small low-density lipoproteins than among 21 controls (108). The small and dense lipoproteins are more atherogenic than the large and less dense lipoproteins. In 15 young and healthy adults, a significant increase in apolipoprotein B, total cholesterol, high-density lipoprotein cholesterol, free fatty acids, uric acid and urea was seen after three weeks on low-carbohydrate, high-fat diet compared to a control group (n=15) (109). Notably, there were considerable individual variations seen in lipid changes.

Since elevated cholesterol is one risk factor for cardiovascular disease, there have been speculations that KDT may increase the risk of atherosclerosis (107, 110). For the general population, in 2017 the American Heart Association concluded that replacing saturated fat with polyunsaturated fat reduces the risk for cardiovascular disease by 30%, while replacing saturated fat with refined carbohydrates and sugar does not reduce the risk (110). There is, however, an ongoing dispute on this topic (111-113). Interestingly, dairy products, although high in saturated fat that increase cholesterol may reduce risk of cardiovascular disease (114, 115). Moreover, whether the absence of carbohydrates in KDT in fact could protect against the atherosclerotic process remain to be investigated.

In the KDT literature, fat types are rarely discussed. However, a Turkish group reported results from 121 children treated with olive-oil based CKD (116). Elevated cholesterol and triglycerides were found, but not as pronounced as in the study mentioned above (107). A direct comparison of these studies was, however, difficult.

A few trials with pseudo-markers for cardiovascular disease as outcome variables have been carried out in children and young adults. The results are conflicting. One study

found that 23 children using CKD had increased arterial stiffness of the carotid artery compared to 20 controls (117). Such changes were also observed by a Swedish group in 26 children using KDT in one year (118). However, these changes were reversed during the second year of treatment (n=13) (118). A group from Turkey published a study claiming that no changes on carotid intima-media thickness and elastic properties of the carotid artery and the aorta could be found in 38 patients after six months on KDT (119). In a study of carotid intima-media thickness in 20 adults using MKD, compared to 21 controls, no significant difference was seen after 12 months of treatment (108). However, methodological weaknesses are found in these studies, and currently no firm conclusions can be made.

Notably, the commonly used AED carbamazepine also affects the lipid profile, and concurrent treatment may therefore be an additional factor (120, 121).

According to our clinical practice, dietary counselling may reverse a diet-induced cholesterol elevation, and after ending the treatment, lipid levels return to normal values within12 weeks (25).

1.4.5 Cardiomyopathy

In rare cases, cardiomyopathy and prolonged Q-T interval in ECG has been reported in children using CKD; sometimes associated with selenium deficiency (122, 123). A recent

study could not disclose any deleterious effect of KDT on cardiac repolarization measures (124).

1.4.6 Kidney stones

Presumably due to the previous mentioned KDT-induced metabolic acidosis, there is an elevated risk of developing kidney stones associated with KDT. At the beginning of this century, kidney stones were reported in 5.4 – 6.9% among children on CKD (125, 126).

Later, in a retrospective study published in 2009, the incidence of kidney stones was reduced to 0.9% due to preventive use of potassium citrate (127). Potassium citrate is also recommended to those who eat a normal diet but who have recurrent kidney stones of calcium oxalate and calcium phosphate, which are the most frequent stone types found among children on CKD (128).

Fluid intake is inversely correlated to the risk of developing kidney stones (128). Fluid restriction is no longer practiced as part of KDT, but in spite of this, many children have limited fluid intake (127). It is our experience that this can also be a problem among some adults, especially those who are intellectually disabled.

Too much fluids should also be avoided, especially when KDT is combined with the AED oxcarbazepine, since hyponatremia is a common side effect of oxcarbazepine, and this may be aggravated by excessive fluid intake.

In our clinical practice with adults using MKD, kidney stones have successfully been prevented. We recommend intake of potassium citrate if the patient has increased risk of developing kidney stones due to one of the following factors: strong familial

predisposition or a previous history of kidney stones themselves, having low fluid intake or co-treatment with carbonic anhydrase inhibiting AEDs. If these risk factors are present when KDT is planned, computed tomography of the kidneys is carried out before starting the treatment. During treatment, uric acid and haematuria are assessed on a regular basis.

1.4.7 Carnitine deficiency

Carnitine is required for transportation of long-chain fatty acids into mitochondria and is therefore essential for energy production from fat. Carnitine is a semi-essential amino acid, and humans are able to synthesise carnitine from the essential amino acids lysine and methionine. Only the L-isomer is biologically active. Dietary sources are those of animal origin, with red meat having the highest content (129). When present in food, around 75% of carnitine is absorbed, while absorption from supplements may be considerably lower (130). From 2 g carnitine daily as supplement only 20% is absorbed (131).

Total or free plasma carnitine concentration is reduced in patients using individual AEDs, especially valproate (103, 129, 130). Risk factors of hypo-carnitinemia in patients with epilepsy are: Usage of multiple AEDs, (including valproate), young age, intellectual disability, and enteral or parenteral feeding without carnitine supplement (130).

It has been suggested that KDT can induce carnitine deficiency, possibly due to the high fat content, but this seems to be a transient reduction that normalise after a few months (103, 129). Children who start with KDT are routinely checked for carnitine values and supplemented if the levels are low (81). In adults, we observed a significant reduction of

free and total plasma carnitine among those using MKD compared to a control group ($p<0.001$ and $p=0.04$, respectively) (37). Some of those who experienced low carnitine levels reported lack of energy and muscle weakness (37).

1.4.8 Bone health

Children and adults treated with several AEDs over many years are at increased risk of developing impaired bone health. Optimal management of weak bone health in patients with epilepsy is still a matter of controversy (132). The frequently used AEDs phenobarbital, phenytoin, carbamazepine, valproate, oxcarbazepine and lamotrigine have all been connected to impaired bone health in this patient group (133). AEDs may either directly affect bone metabolism or indirectly via an interaction with vitamin D metabolism.

The KDT may impose an additional risk of impaired bone health caused by the acidity of ketone bodies, altered vitamin D metabolism and lowered growth factors caused by the diet (81, 134). Bergqvist and co-workers showed progressive loss of bone mineral content caused by CKD in children (100). Recently, an Australian group found similar results (135). However, a long-term follow-up (24 months) of 38 Swedish children on MKD showed no negative effect of the dietary treatment on bone mass (136).

Data on reduced mineral density caused by KDT in adults is currently lacking. But as for all patients treated with AEDs on long-term basis, prophylactic calcium and vitamin D supplementation and regular monitoring of bone health using dual-energy X-ray absorptiometry (DXA), is recommended (133).

1.4.9 Growth retardation

Impaired growth is commonly seen among children using long-term CKD (81). A study of 22 children showed a correlation between ketosis and growth retardation (137). Decrease in insulin-like growth factor-1 may be a causative explanation (137).

Whether a reduced protein intake associated with CKD could cause reduced growth has been discussed, and findings are mixed. In a study comparing growth in 75 children on either CKD or MCT diet - the MCT diet provided higher protein intake than the CKD - no difference in growth could be observed after 12 months (138). A retrospective Australian study of 35 children revealed that less than 1.5 g protein/100 kcal was associated with reduced growth (139).

Suggestive of less severe side effects of MKD than CKD, a 2-year follow-up of 38 Swedish children on MKD with mean age 6.1 years showed no negative effects on growth (136).

One year after having stopped the diet, a catch-up growth was seen (140).

1.4.10 Menstrual disturbances

Menstrual disturbances are frequently seen in women using KDT. The frequency of such disturbances possibly increases with increasing ketogenic ratio. In 1930, Barborka reported of amenorrhea in 12 (21%) of the 56 women treated with CKD for 12 months (16). Sirven and co-workers studied eleven adults using CKD, and all nine female patients (100%) had menstrual irregularities such as missed or irregular cycles (21). Females using MKD are less commonly reported to develop menstrual irregularities; in one paper one in 17 female participants (6%) had menstrual disturbances (28). In

another report of nine women who had menstruation and using MKD, one (11%) experienced longer and irregular periods and increased discharge (37). Thus, in women with KDT start and end of menses periods should be recorded routinely (32).

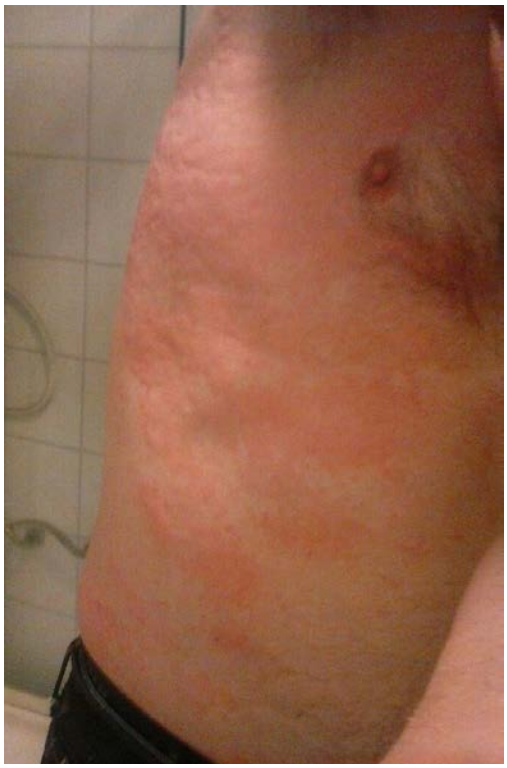
1.4.11 Other reported side effects

There are reports of rare and sometimes fatal side effects of the KDT. However, one should bear in mind that many of the patients attempting a KDT have serious underlying conditions with multiple comorbidities, severe epileptic encephalopathies, or other severe epilepsy syndromes with unknown aetiology. In a study reporting side effects from 129 children using CKD, four patients died during the treatment (102). Two died from sepsis, one from cardiomyopathy, and one from lipoid aspiration pneumonia.

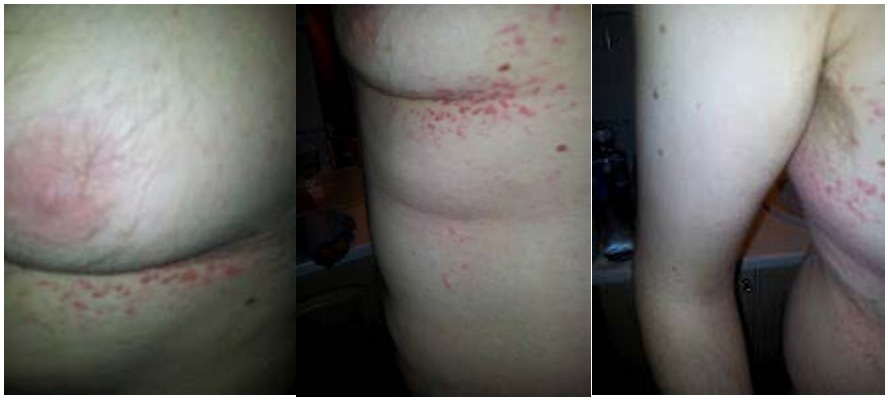
Pancreatitis has been reported (102, 141), a few cases of hepatic failure likewise. KDT combined with valproate may increase the risk of these adverse effects (42, 102, 142).

Payne et al. described one adult patient who developed a psychosis during dietary treatment (30).

Among our patients on MKD (not published), three experienced debut of food allergy occurring simultaneously with diet start. Of these, two achieved severe skin rash for which one was hospitalised and the diet was terminated (Pictures 1-2), with permission.



Picture 1. Severe rash that occurred immediately after starting MKD.



Picture 2. Young male with rash associated with MKD.

1.5. Metabolic aspects of ketogenic diets

Ketosis induced by dietary changes or fasting are conditions to which the metabolism adapt and should not be confused with ketoacidosis which can be a life threatening condition during the course of diabetes mellitus. Ketosis arising during fasting or eating a diet low in carbohydrate is termed metabolic or nutritional ketosis (143).

During periods of fasting the human body adapts efficiently, and the ability of cognitive preservation during periods with little or no food available must have been an important factor of evolutionary selection. During the first 24 – 48 hours of fasting, the main fuel switches from glucose to fat and metabolic and hormonal changes are evident. Hormonal and regulatory changes bring about fatty acid release from fat stores, fatty acids are used as fuel for skeletal muscles, and ketones become present in blood and urine. Blood glucose is reduced, less insulin excreted, while the levels of glucagon and cortisol increase. In obese individuals, the production of ketones may amount to 150 grams per day, and the concentration of blood ketones stabilise at 7 mmol/L after 17 days (144). A key regulator of ketogenesis is the nuclear receptor peroxisome proliferator receptor alpha (PPARα). It acts as a switch that facilitates the up-regulation of all enzymes that are necessary for ketogenesis. Hepatic ketogenesis is induced by coordinated up-regulation of around 20 enzymes and reaches a steady state after 30 days (145).

When eating a diet high in fat and with as little as 10 – 20 grams of carbohydrate per day, a metabolic condition similar to fasting occurs. But unlike fasting, necessary energy and nutrients are available and duration can be long lasting.

1.5.1 Ketones

Ketones are water soluble substances containing a group of one oxygen atom connected to two carbon atoms by double bonds. Ketolysis is the break-down of ketones to produce adenosine triphosphate (ATP) - a molecule that captures energy, carbon dioxide and water. There are three endogenous ketone bodies: acetoacetate, beta-hydroxybutyrate and acetone. Beta-hydroxybutyrate has been named a super-fuel (146). This is because it produces more ATP than alternative substances such as glucose and pyruvate. Also, the electron transport chain is less likely to generate free oxygen radicals and probably reduce more glutathione when metabolising ketones compared to glucose (146). These characteristics may be of special value in trying to explain the efficacy of the diet in epilepsy and other brain diseases.

1.5.2 Brain energy

When eating a normal diet, the brain is mainly fuelled by glucose, and the brain oxidises around 120 grams of carbohydrate daily, which accounts for about 20% of energy consumed by the whole body (147). Whether free fatty acids can be utilised as brain energy has been questioned for many years. However, recent research has revealed that free fatty acid transport across the blood-brain barrier is slow and inefficient (148).

When using KDT glucose availability is vastly reduced and the preferred fuel for the brain is ketones. About 55 - 60% of the brain energy requirements can be met by ketones from the blood, while free fatty acids are a minor energy contributor (148, 149).

Ketones are transported across the blood-brain barrier via the monocarboxylic acid transporter 1 (148).

The two main cell types in the brain are neurones and glia cells. Neurones perform the complex tasks of signal transmission, while glia cells support the neurones. These two cell types work together tightly and coordinated (150). For example, neurotransmitters may be excreted into the synapse by neurones and removed from the intercellular space by glia cells. Cycling of substances such as neurotransmitters, ions, amino acids and nutrients take place. Glia cells are organised in networks communicating via connexin gap junction channels, and through these channels substances such as ions and nutritional substances are transmitted (151). Glia cells, but not neurons, have the ability to produce ketones from free fatty acids (148). Both neurons and glia cells, and the communication between these cells, may be implicated in the seizure reducing mechanisms of KDT (151).

1.6. How do ketogenic diets work?

Despite that KDT has been in use for nearly a century, we do not know the exact mechanisms by which it provides seizure protection in people with epilepsy.

Epilepsy is a disorder characterised by increased neuronal excitability in a cerebral neuronal network, and several factors may influence such excitability. As the diet imposes a fundamental shift in the energy metabolism of neurons and glia cells which is likely to influence the seizure threshold, there are probably not only one but several mechanisms of action working together (152-154).

In this section, I will give some examples of putative mechanisms of action, but no attempt is made to cover all the proposed mechanisms.

1.6.1 Response based on genetics

The suggested underlying mechanisms of action can be divided into two groups: 1) mechanisms that address one specific genetic defect and 2) general mechanisms that may raise the seizure threshold in epilepsy of any cause.

One example where aetiology is straight forward and effect of the KDT is readily understood is the Glucose transporter protein 1 deficiency syndrome where the blood-brain barrier glucose transporter is dysfunctional. Switching from glucose to fat-derived ketones as main brain fuel is the first-line, life-long treatment of this genetic disease, and most patients respond very well, although exceptions exist (59).

Pyruvate dehydrogenase deficiency is another monogenic disease where the enzyme converting pyruvate to acetyl-CoA is malfunctioning (60). KDT is the main treatment for this condition and the mechanism of action can readily be understood; by supplying ketones instead of glucose, pyruvate is bypassed and the defect enzyme converting pyruvate to acetyl-CoA is not needed. However, the clinical response to KDT does vary between individuals, presumably at least partly due to different mutations (141).

In severe cases of developmental disorders or epileptic encephalopathies, underlying monogenic causes have been detected the recent years. Patients with mutation in the same gene frequently show a great variety of clinical presentations. Moreover, the response to KDT is highly variable. However, some patients suffering from several of these syndromes respond extremely well to KDT (81).

In a study from South Korea, 333 children with severe epileptic encephalopathies were analysed for 172 different genes related to such disorders (155). Of the 333 children, 155 had tried ketogenic diet, and response was defined as >90% seizure reduction. Patients with mutations in the genes *SCN1A* (n=18), *KCNQ2* (n=6), *STXBP1* (n=4), and *SCN2A* (n=3) responded excellently to the dietary treatment, while patients with mutation in *CDKL5* (n=10) did not show any effect (155).

Interestingly, a recent genome-wide mega analysis mapping genes from 15212 individuals with epilepsy and 29677 controls, revealed a considerable overlap between associated genes in focal and generalised epilepsies and the above mentioned genes involved in monogenic epileptic syndromes. Furthermore, the authors found several new genes associated with genetic generalised epilepsies (156).

In a considerable number of patients with epilepsy, an underlying genetic predisposition and that they develop epilepsy after an acquired brain insult such a trauma or infection is assumed (157, 158). In these patients, one could speculate that general seizure reducing mechanisms of KDT could be applicable, but also mechanisms that specifically interact with the genetic predisposition.

1.6.2 Direct effect of ketones and polyunsaturated fatty acids

Ever since the diet was introduced, a direct seizure attenuating effect of ketone bodies has been suggested to be the mechanism of action of the diet. In patients whose epilepsy was completely controlled by diet, the endogenous ketones acetone, acetoacetate and beta-hydroxybutyrate have been traced in the blood and in cerebrospinal fluid (159). According to two reports, the blood level of beta-hydroxybutyrate, but not urine

ketones, is correlated to the seizure reducing effect (160, 161), but this has not been confirmed by others (67). Kossoff and Rho suggested that a lower limit of ketosis is required to achieve seizure reduction (162).

Applying acetone and acetoacetate to epilepsy animal models have demonstrated that these compounds have antiepileptic properties (163). However, it is not yet confirmed whether these findings can be transferred to human disease (164).

In children using KDT, a correlation has been found between an increased level of polyunsaturated fatty acids in serum and a seizure reducing effect (159).

1.6.3 A modulation of neurotransmitters

Ketogenic diets may modulate the levels of neurotransmitters. In 2005, Yudkoff and co-workers launched a hypothesis connecting the shift in energy production, due to ketones substituting glucose as the main cerebral fuel, to a change in neurotransmitter function (165).

The hypothesis, which was strengthened in a rat model, claims that the metabolism of ketones compared to glucose through the tricarboxylic cycle consume oxaloacetate at a higher rate. In glia cells, ketosis may enhance the transfer of glutamate to glutamine via the enzyme glutamine synthetase (166). Reduced availability of oxaloacetate leads to reduced formation of aspartate and higher concentration of glutamate in neurons. Glutamate is a precursor for GABA, and increased concentration of glutamate presumably increases the production of GABA, the main inhibiting neurotransmitter.

Some clinical data may support the hypothesis. Dahlin et al. have measured amino acid levels in cerebrospinal fluid in 26 children using KDT (167). They measured diet-induced changes in several amino acids, and for threonine there was a significant correlation with the seizure reducing response. Moreover, GABA levels were higher in the responders, i.e. those who achieved >50% seizure reduction, than in non-responders. In those with >90% seizure reduction, GABA levels were significantly higher both at baseline as well as during the diet. Furthermore, Wang and co-workers used two-dimensional double-quantum MR-spectroscopy and measured an increase of GABA levels in patients before and after starting the KDT (168).

1.6.4 Ion channels

In a study of the influence of ketones on voltage-gated Shaker K^{+-} channel expressed in Xenopus oocytes, polyunsaturated fatty acids and cerebrospinal fluid from children using KDT showed that clinically relevant concentrations of polyunsaturated fatty acids and cerebrospinal fluid affected the ion channel in a seizure limiting way (169).

Of patients diagnosed with Dravet syndrome, 70-80% have a known mutation in a voltage-gated sodium channel (*SCN1A*), and many of these patients respond very well to dietary treatment (170). Also in *SCN1A* knock-out mice the diet has been shown to reduce seizures (171).

In 2007, a group at Harvard Medical School suggested that the seizure reducing effect of ketones in rats was mediated by an ATP-dependent K^+-channel (172, 173). Ketones are metabolised in the tricarboxylic cycle, and glycolysis become less active when ketones become the main fuel. The channels reside on the cell membrane and may thus be more

prone to glycolytic derived energy which is released in the cytosol than to energy produced by the tricarboxylic cycle residing inside the mitochondria. ATP-dependent K^+-channels are activated when ATP levels are low and inhibited when ATP levels are high. When activated, these channels generate a hyperpolarising current that reduces cellular excitability and may thereby increase the seizure threshold (173).

1.6.5 Enhanced energy situation

Glucose transporter protein 1 deficiency syndrome is caused by mutations in the *SLC2A1* gene. The mutation gives impaired glucose transport across the blood-brain barrier (59). The compromised energy to the brain of these patients may cause various neurological problems, including epileptic seizures. These problems may vanish completely when ketogenic diet is initiated. The Glucose transporter-1 deficiency syndrome is a rare condition, but impaired brain energy metabolism has been hypothesised as a cause or perpetuating factor in patients with drug-resistant epilepsy (174).

A recent review highlights how impaired energy metabolism in epileptic foci may be resolved by several of the proposed mechanisms of action of the ketogenic diet (151).

Impaired oxidative phosphorylation may increase reactive oxygen species (ROS), reduce ATP production and cause epilepsy (175, 176). Interestingly, KDT is effective in syndromes associated with defects in the mitochondrial respiratory chain enzyme complexes (177).

The switch from glucose to fat-derived ketones as main cerebral fuel has been shown to improve the cellular energy metabolism in the brain. This cannot be overlooked since the theoretical causality is striking (178). Bough et al. showed that a majority of rat genes affected by KDT were related to oxidative phosphorylation. Moreover, they detected a diet-induced 46% increase of mitochondria density (178).

1.6.6 MCT fatty acids

The MCT ketogenic diet has similar seizure reducing effect as the CKD (33). MCT oil consists of short chained fatty acids, mainly C_8 and C_{10} (179). Recently, a direct antiepileptic action of decanoic acid (C_{10}) has been described (180). It works by binding to the AMPA receptor and thereby reducing its activity. This is a similar mechanism of action as perampanel, a new AED, but C_{10} and perampanel bind to different seats on the receptor. This could be one seizure reducing mechanism of the MCT-diet. Moreover, pure decanoic acid could exert a seizure reducing effect on its own used as a supplement, without being a part of ketogenic diet (179).

1.6.7 Gut microbiota

The gut consists of a wide variety of bacteria, and until recently the function of the microbiota for human health has been largely ignored. However, the interest in this topic is increasing; the connection between gut function and brain is taking on (181).

A mouse study published in 2018 indicated that ketogenic diet might exert its antiepileptic effect via the microbiota. The study had a thorough design and showed in a convincing way that the diet-induced changes in microbiota caused an increase of GABA levels in hippocampus (182).

1.6.8 Metabolic regulation

The improvement in seizure frequency is reported to become apparent 2–8 weeks after diet onset (23). Thus, adaptive changes in gene expression can be involved in the antiepileptic effect of the diet. During the first weeks after switching macronutrient intake to high-fat, low-carbohydrate some metabolic pathways are up-regulated, while others are down-regulated. One important regulator of this switch is the transcription factor PPARα, also called a "lipostat" transcription factor. PPARα acts similar to hormonal receptors in hepatocytes, but unlike other hormonal receptors PPARα is activated by a whole range of fatty acids, many of which are elevated by KDT (145). Furthermore, PPARα up-regulates the rate limiting enzyme for ketogenesis namely 3-hydroxy-3-methylglutaryl-CoA synthase. PPARα and 3-hydroxy-3-methylglutaryl-CoA synthase are expressed in astrocytes indicating that astrocytes produce ketone bodies as fuels for neighbouring neurons (145). This means that effect of PPARα regulation could occur in the brain and execute a possible anti-seizure effect. Although somewhat speculative, Cullingford suggests several downstream effects of PPARα activation, and that several AEDs may exert its effect through this mechanism. Furthermore, PPARα indirectly inhibits the expression of cyclooxygenase 2 (183).

PPARα polymorphisms may also play a role in predicting who will respond to KDT (184). Modifications to the fatty acid profile of the ketogenic diet may directly modify

PPARα-activating molecules in brain, potentially providing a broader spectrum of antiepileptic effect (184).

As a prominent regulator of anti-inflammatory and anti-oxidative gene products, the sister receptor PPARγ has also been proposed to exert direct antiepileptic effects (185).

1.6.9 Epigenetics

Clinical experience indicate that children who respond well to KDT and who remain on the diet for at least two years may retain the seizure reducing effect after tapering the diet. This could be interpreted as the diet may impose not only an antiepileptic effect, but also an *antiepileptogenic* effect, i.e. having a disease modifying effect. One possible explanation to this effect is that the KDT may cause epigenetic modifications, such as DNA methylation or histone modification, regulating gene expression (186). Future research will reveal whether this exiting hypothesis will be strengthened further.

1.7. Why did we run this project?

In 2010, when we planned this project, except for the Barborka study from 1930, only four papers reporting prospective trials of KDT in a total of 58 adults with drug-resistant epilepsy had been published (Table 1A). Of these four papers, two were based on MKD and two on CKD. The seizure reducing effect among these studies varied from 13 to 54%. Also diet types gave different responses; 22-54% and 13-33% achieved >50% seizure reduction on CKD and MKD, respectively. The results were interesting, but the data was too sparse and the methods too week to draw any conclusions among the adult population. Moreover, the study by Neal et al. had shown that such treatment was effective in children (20).

Given the demand for more treatment options among the patient group, we found it important to study whether KDT could be tolerated and of benefit to adults with drug-resistant epilepsy.

Although the CKD could be more efficient and an intervention period of six months would be preferable, taking into account the high drop-out rates from the previous studies, it seemed more feasible to choose the MKD and to limit the intervention period to three months. The RCT design would give the necessary strength to conclude on efficacy and was therefore chosen.

CHAPTER 2: AIMS OF THE STUDY

The overall aim of this project was to study the effects of modified Atkins diet on seizure frequency in the treatment of drug-resistant epilepsy in adults.

The aims were:

- To assess the efficacy and tolerability of adding a modified Atkins diet to current drug treatment in adults with drug-resistant focal and generalised epilepsy (Paper 2 & 3)
- To study whether adding a modified Atkins diet to current drug treatment may have an impact on serum concentrations of AEDs (Papers 1 & 4)

CHAPTER 3: PARTICIPANTS AND METHODS

3.1. Study population

This thesis is based on results from an intervention study carried out at the National Centre for Epilepsy from March 2011 to March 2017. A total of 277 patients from all of Norway were screened, and 88 participants were enrolled. Figure 1 gives an overview of the patients included in Papers 2 - 4. Inclusion and exclusion criteria are listed in Paper 3, page 1568.

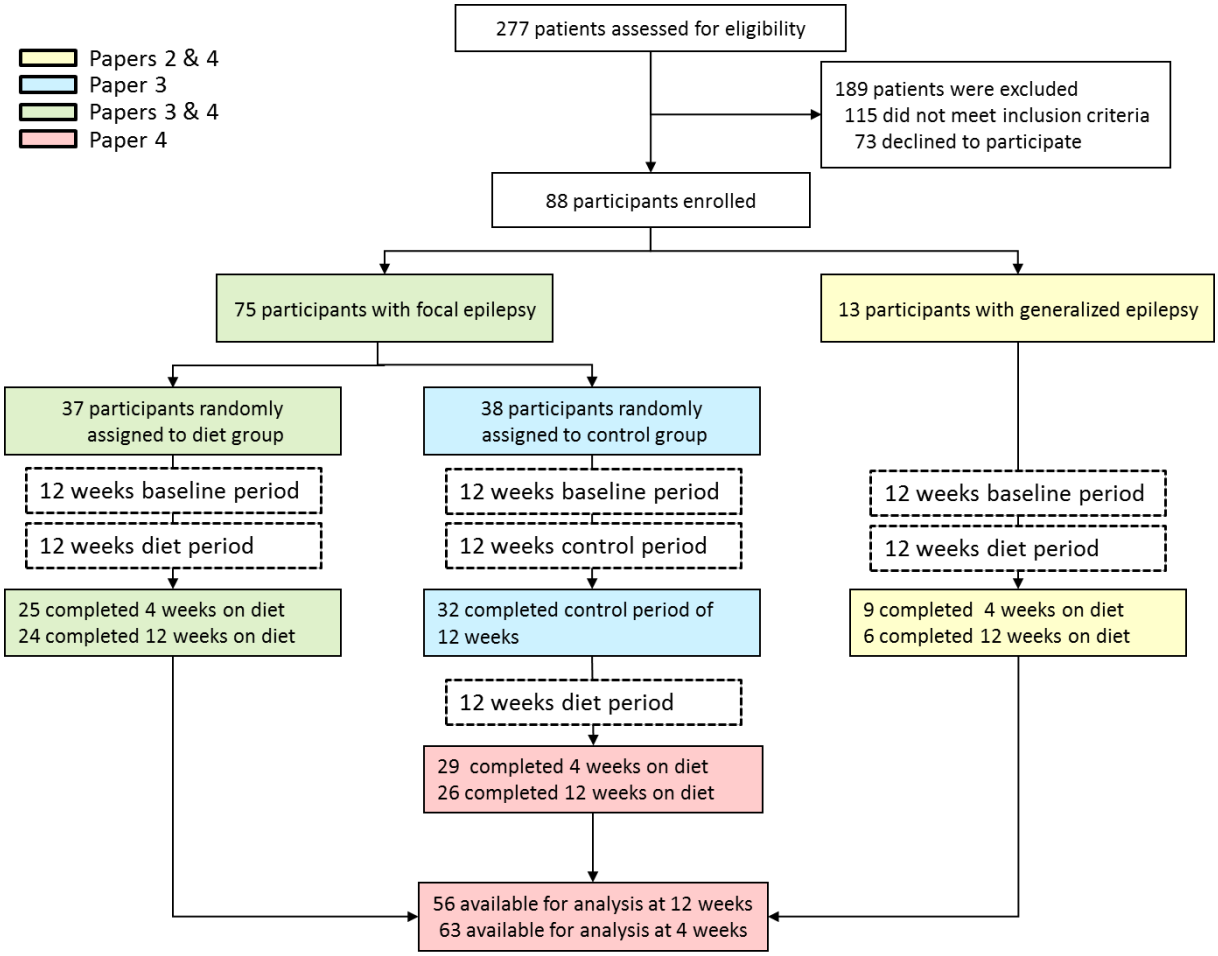


Figure 2. The figure gives an overview of the participant flow in Papers 2-4.

3.2. Study design

The study consisted of two parts: 1) a prospective study of patients with *generalised* epilepsy, and 2) a randomised clinical trial (RCT) of patients with *focal* epilepsy. All participants, also those allocated to the control group in the RCT, were offered dietary treatment in accordance with the same protocol.

3.3. Approval

The study was approved by the Regional Committee for Medical and Health Research Ethics in South-East of Norway (2010/2326) and registered with ClinicalTrials.gov (ID NCT01311440). All participants gave written consent to take part.

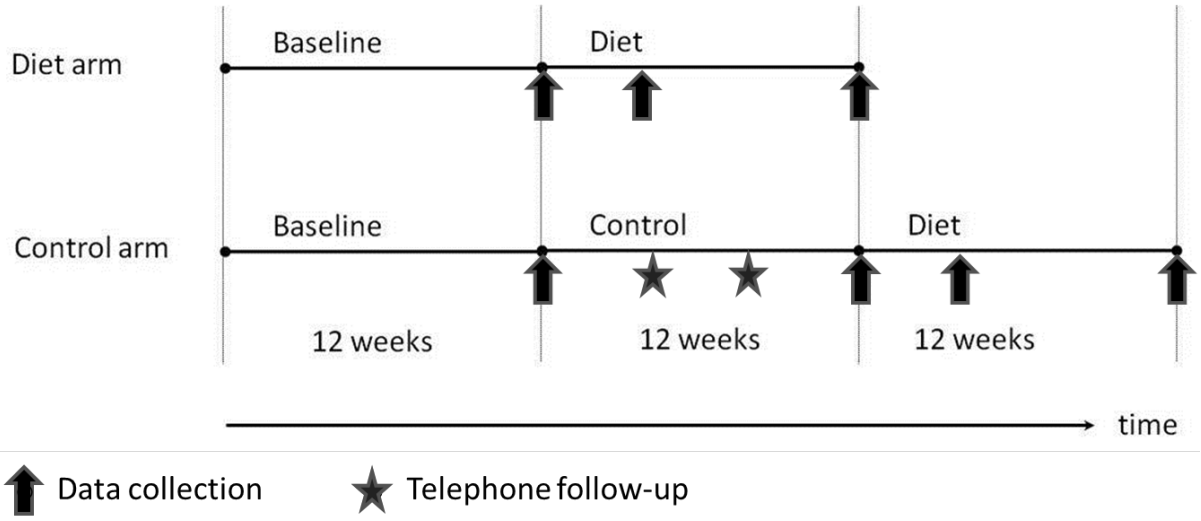


Figure 3. The figure shows the study arms and the point of time for data collection.

3.4. Procedures and randomisation

Participants completed a 12-week baseline period consuming their habitual diet and recording seizure frequency before starting the 12-week dietary treatment, i.e. eating a MKD, (Figure 3). Those randomised to the control group of the RCT took on another 12-week period of seizure recording while eating normal diet before starting the dietary treatment. In paper 4, the second 12-week period on normal diet, i.e. the one

immediately preceding the diet period, was chosen as baseline for those who had been randomised to the control group. Data collection was carried out before the intervention periods, and 4 and 12 weeks after starting the dietary treatment.

The procedures of baseline and intervention periods for both diet and control arms are described in detail in paper 2 pages 198 and paper 3 pages 1568-9. The randomisation procedure is described in paper 3, page 1568.

3.5. Assessments

3.5.1 Demographics

Clinical data such as age, gender, epilepsy type and epilepsy aetiology, seizure types and frequency, age at epilepsy onset, number of previously tried AEDs, previously tried other treatment options, current treatment, and MRI findings were obtained from the patients' electronic hospital record and by interviewing the patients and/or the caretakers.

3.5.2 Seizure frequency

Seizure frequency was the primary outcome of the dietary intervention. The ability to register seizures either by the patient or, in case of disabled persons, by caretakers, was a criterion for inclusion. Classification of the seizures was done by a neurologist and was based on clinical observation of seizure semiology and inter-ictal and ictal EEG-findings. In the case of multiple seizure types and high seizure frequency, an agreement was made with patient or caretakers about which seizures to register. The seizure diary is given in Appendix.

To evaluate the change in seizure frequency, we compared the average weekly seizure frequency in the baseline period to the average weekly seizure frequency the last eight weeks of the intervention period.

3.5.3 Adverse effects

To detect adverse effects of the dietary treatment, thorough interviews of the patients and/or the caretakers were carried out after 4- and 12-week intervention.

3.5.4 Seizure severity and quality of life

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)(187), and the revised Liverpool Seizure Severity Scale (scale: 1–100 points, score reduction indicates reduced severity) (188). The forms were filled in by participants during the hospital admission, but the questionnaires were not facilitated for intellectually disabled persons. Both questionnaires are included in Appendix.

3.5.5 Dietary records

During three days, participants recorded the weight or volume and detailed description of all foods and beverages consumed during two weekdays and one weekend day. Food records were completed at home preceding 4 and 12 weeks of dietary treatment and collected during the hospital admissions. The control group recorded dietary intake of their habitual diet once during the control period. The Norwegian food composition database 2012 – 2017 (189), was used to calculate the daily intake of energy (kcal), fat

(g), protein (g) and carbohydrate (g). Ketogenic ratio was defined as grams of fat/protein + carbohydrate.

3.5.6 EEG recordings

A standard EEG examination was carried out in all participants before and after 12 weeks of dietary treatment.

3.5.7 Weight

Body weight was recorded at each point of data collection. It was done by nursing staff during admission in the morning after an overnight fast and before breakfast.

3.5.8 Biological sampling and analysis

Food and drug fasting blood samples were drawn in venous blood at each point of data collection. Details are reported in Papers 2-4.

To evaluate diet adherence, blood and urine ketones were assessed both at home and during hospital admission. Urine ketones were assessed twice daily (morning and evening) in the 12-week intervention period using urine dip-sticks. The colour of the dip-stick corresponds to a number given on the pack-label. At home, the number was recorded in the seizure frequency form, while during the hospital admissions it was recorded by a nurse in the patient record. Also, during admissions, the extent of blood ketosis and glucose, based on a finger-prick blood sample, was obtained twice (morning and evening) using blood ketone/glucose test strips. These were recorded by a nurse in the patient record.

3.6. Statistical analyses

In all the papers, the statistical tests were two-sided and a 5 % level of significance was used. Assumption of normality was checked by visual inspection of Q-Q plots and by the evaluation of skewness of the variable. Appropriate non-parametric and parametric tests were used accordingly.

The distribution of seizure frequency was skewed and for the RCT (Paper 3) the Hodges-Lehmann estimator was used to estimate the difference in medians between the diet and control groups (190). Further details of the statistical analysis are described in each paper.

Statistical analysis was performed using IBM SPSS Statistics (IBM Corporation, NY 10504–1722, USA) version 21-25.

CHAPTER 4: SUMMARY OF RESULTS

4.1. Paper I: Modified Atkins diet may reduce serum concentrations of antiepileptic drugs

During treatment of the first 20 participants of the study, we observed a reduction in serum concentrations of AEDs after 4 and 12 weeks of treatment compared to baseline. In this paper we presented four of these patients who experienced considerable reduction in serum concentrations of AEDs. After 12 weeks on the diet, the average serum concentrations of the respective AEDs were reduced by 35% (range 6–46%) compared to pre-diet values. We suggested that an interaction between diet and drugs could be of clinical significance, but a larger data set was needed to conclude.

4.2. Paper II: A prospective study of the modified Atkins diet for adults with idiopathic generalized epilepsy

Thirteen patients (12 women) with drug-resistant generalised epilepsy, nine of whom had juvenile myoclonic epilepsy (JME) were treated with MKD. Six participants, all with JME, completed the 12-week study period, and of these, four experienced >50% seizure reduction. Also, their seizure severity was reduced, quality of life considerably improved, and their body weight was reduced. However, lack of motivation, poor compliance, and seizure aggravation were the main reasons for premature termination of the diet. In three of the four responders, the benefits of the diet were so considerable that they chose to continue the treatment. This paper contributes to the documentation on whether people with drug-resistant genetic generalised, and particularly JME, may benefit from KDT.

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

This paper presents the main results from the RCT in adults with drug-resistant focal epilepsy treated with MKD adjunctive to other therapy (Table 4). The primary endpoint was a change in seizure frequency after 12 weeks of intervention. We randomised 37 participants to dietary treatment and 38 to control group. For intention-to-treat analysis, data from 28/34 participants was available in diet/control groups, respectively. When reporting on-treatment analysis, four who did not complete the intervention in the diet group and two who did not deliver complete seizure record in the control group were excluded, leaving 24 vs. 32 participants in data vs. control group.

Table 4 Participants who achieved cut-off points

Intention-to-treat analysis				
% seizure reduction	Diet group (n=28)	Control group (n=34)	Relative Risk (95% confidence interval)	p-value
>50	3 (11%)	2(6%)	1.8 (0.3-10.2)[1]	p=0.65[1]
>25	10(36%)	5(15%)	2.43 (0.94-6.28)[2]	p=0.06[2]
≤25	18(64%)	29(85%)		
On-treatment analysis				
	Diet group (n=24)	Control group (n=32)	Relative Risk (95% confidence interval)	p-value
>50	3 (13%)	2(6%)		n.s
>25	10(42%)	5(16%)	2.67 (1.05-6.79) [2]	p=0.03[2]
≤25	14(58%)	27(84%)		

[1] Fisher's exact test
[2] Chi-square test

There were large individual variations in seizure response, possibly negatively influenced by a reduction in serum concentrations of AEDs.

4.4. Paper IV: Pharmacokinetic interaction between modified Atkins diet and antiepileptic drugs in adults

We wanted to examine in more detail the possible influence of MKD on serum concentration of AEDs. We had prospective data from 63 adult patients, including the 13 from Paper 2 and the control group from Paper 3. We compared AED serum concentrations, ketones, glucose and haemoglobin A1c before and after the 12-week dietary intervention. We found significant reduction in mean serum concentrations of carbamazepine, clobazam, and valproate after 4 and 12 weeks of the diet period ($<0.001 \leq p \leq 0.02$). Serum concentrations of lacosamide, lamotrigine and topiramate were

less reduced (0.02≤p≤0.08), while the serum concentrations of oxcarbazepine, zonisamide and levetiracetam were unchanged (0.06≤p≤0.90).

In accordance with the results from paper 3, we found a statistically significant reduction in serum concentration after 4 and 12 weeks of all drugs taken together.

Percent change in serum concentration of AEDs was, however, not significantly correlated to percent change in seizure frequency after 12 weeks of dietary treatment (r=0.14, p=0.33, n=53), but it was negatively correlated to urine ketosis (r=-0.43; p=0.003; n=46); the higher ketosis, the more prominent drop in serum concentrations of the AEDs.

In this paper we also published data on the diet-induced change in ketosis, proposing that an adaption to ketosis takes place after four weeks on the MKD (Figure 4).

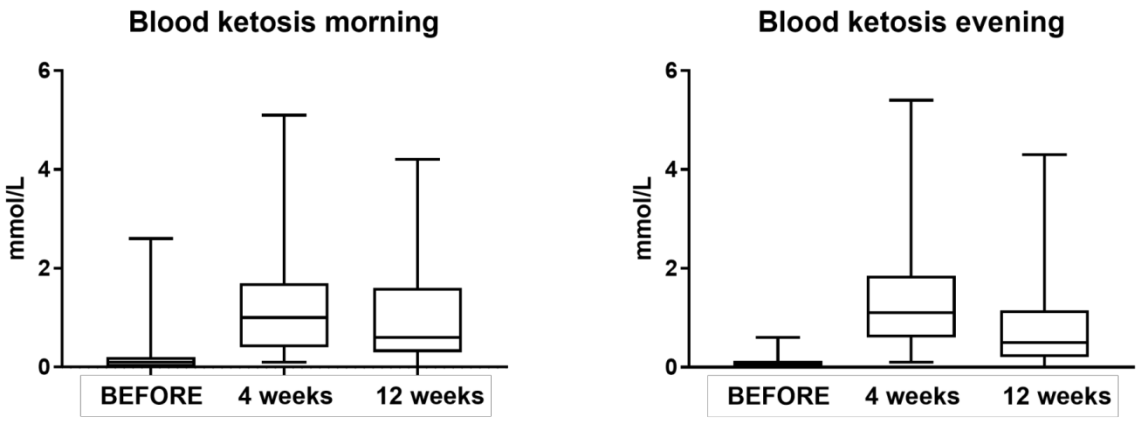


Figure 4. Mean ketosis in blood, morning (n=51/46) and evening (n=50/45) assessed before and after 4 and 12 weeks on diet. Values are shown as box-plots.

CHAPTER 5: DISCUSSION OF MAIN FINDINGS

5.1. The main results of the studies:

- In four of thirteen adult patients with drug-resistant generalised epilepsy, all diagnosed with juvenile myoclonic epilepsy, a MKD for 12 weeks led to a clinically relevant reduction of seizure frequency
- In an RCT including 75 patients with drug-resistant focal epilepsy, comparing seizure frequency in 37 patients on MKD against 38 patients with no change in treatment, we found no significant seizure-reducing effect. However there were considerable individual variations in seizure response, and the diet was beneficial to some patients. In the on-treatment analysis the diet group had a moderate benefit (>25% seizure reduction) compared to the controls
- KDT may reduce the serum concentrations of some AEDs
- Treatment with MKD as adjuvant to conventional AEDs was well tolerated ; we detected no serious adverse events

5.2. Why did our results deviate from the results of other studies in this field?

The studies on dietary treatment in adults in current literature are summarised in Table 1. Most of these studies were prospective intervention studies, a weaker design than RCT. The only other RCT on adults, published in 2017, was from Iran (Table 2).

As shown in Table 1, the response to the treatment varies considerably between the studies. However, in our RCT we found a weaker seizure reducing effect than in previous

studies (Table 4). There are many possible explanations to this, which will be discussed below.

Methodological differences between RCT design and prospective design are obviously of importance. It is addressed in Chapter 2 on methodological considerations.

First I will discuss other possible explanations why the previous studies have found better effect of KDT in adults than we did. In the Iranian RCT there are some methodological concerns. Cultural and economic differences between Norway (and other western countries) and developing countries, could be of importance. Moreover, criteria for drug-resistance are not necessarily comparable between the studies. Also, patients with focal epilepsy may respond poorer than those with generalised epilepsy. Lastly, studies using the MKD and the CKD may not be comparable.

5.2.1 Could the RCT from Iran have overestimated the true effect?

The RCT from Iran showed a 35% response rate. This needs some comments, since it is the only RCT published in addition to ours (36): 1) The study was carried out in 2010-12 and was published in 2017. 2) How the patients were recruited to the study is not revealed. That means we do not know how many were invited to take part and how many who declined. Were the participants selected in any way? 3) The baseline period was only one month. This is a very short time of observation. 4) Compared to our patients, the seizure frequency was lower and seemed to have a Gaussian distribution. This was not the case for our patients. Did they register only selected seizure types? The combination of low seizure frequency and short follow-up time may have given invalid results. 5) Epilepsy aetiology of the participants is not stated. 6) Drugs and other

treatment are “changed when necessary throughout the study period”. This means that other treatments than the diet could have had an impact on the results. 7) None in the control group experienced change in seizure frequency. Did they really record seizures, or did they assume there was no change? 8) The authors state one weakness of the study being “two groups were not similar according to antiepileptic drug therapy”. This is however not elaborated any further (36).

Given the questionability of this report, the results could be biased and the efficacy over-estimated.

5.2.2 Cultural differences

There are differences in how to conduct studies and in how to communicate with patients between different parts of the world. In Norway we will tell the patient that we cannot know in beforehand who will benefit from the diet, while Eric Kossoff from Johns Hopkins Hospital in Baltimore, USA may say: “We know it helps” (e.g. we think it will really help your child…) (personal communication). Such differences in the way to address the patients may result in differences regarding the extent of placebo effect.

The study from India has relatively high rate of responders (34). In their results, however, many in the control group also responded. We must bear in mind that India is a low-income country with less resources to spend on health services than Norway. There may be several reasons why they find a better effect of the diet: 1) Fewer drugs are available, and the attempted drugs may not have been the most suitable; thus all included in the studies may not have been drug-resistant. 2) Participants may want to express their gratitude to the physician by having a good effect of the treatment.

5.2.3 Drug-resistance

Our patient population in the RCT was highly drug-resistant as they had tried on average 9-10 AEDs before entering this study. Some other studies where participants achieved better effect of the diet than us may not have had the same degree of drug-resistance. As mentioned, in 1930, when Barborka published his results, only two drugs were available. Also in the study by Cervenka and co-workers from 2016, a considerable number of the subjects were not drug-resistant (32).

5.2.4 Epilepsy aetiology

As data on more patients using KDT are published, it will be possible to compare response to the treatment related to epilepsy aetiology. In a publication by Nei from 2014 (and Sirven from 1999), it was speculated that those with symptomatic generalised epilepsy (this term is outdated and needs translation to today's classification) may have better effect among adults (21, 29). It was not found to be statistically significant although 64% of those with symptomatic generalised epilepsy had a ≥50% seizure reduction, while 28% with focal epilepsy had ≥50% seizure reduction (29). Those with so-called symptomatic generalised epilepsy may have single gene mutations, of which some are known to respond well to dietary treatment according to a study by Ko et al. (155).

Furthermore, it has been speculated that both children and adults with genetic generalised epilepsies respond better to KDT than those with focal epilepsies, but more data are needed to conclude (31, 191-193).

5.2.5 Better efficacy with CKD than with MKD?

There is a controversy on whether CKD with ketogenic ratio 4:1 may give better seizure reduction than a diet with lower ketogenic ratio such as the MKD we used in our project. Of the studies in Table 1, two used CKD with ratio 4:1, two used CKD with ratio 3:1, one used a mix of CKD and MCT-diet, six used MKD, one used both CKD and MKD. The ketogenic ratio of MKD is in the range from 1:1 to 2:1. Given these small studies with such diverse epilepsy aetiologies, seizure types and diet types, the data is too weak to even speculate that a variance in ketogenic ratio may be decisive for the results. However, there are some indications that some children may respond to CKD and not to MKD (69). Therefore we cannot rule out the possibility that some of our non-responders could have responded to a CKD with ketogenic ratio of 3:1 or 4:1.

5.3. Diet-induced seizure aggravation

In our RCT, three patients dropped out early due to seizure aggravation. Another three experienced a considerable seizure exacerbation but completed the study period. This means that six (21%) of the 28 in the diet group who started the diet experienced an increased seizure frequency. This has been described also by others, but to my knowledge not to the same extent (16, 30, 47, 48). However, in prospective studies, cases such as the three who dropped out early due to seizure aggravation would not necessarily have been accounted for.

Due to the small sample size in our RCT, we cannot determine the true number of adults who may risk a diet-induced seizure aggravation.

Our prospective study of people with drug-resistant epilepsy (Paper 4), five (9%) of 53 had an increased seizure frequency of more than 50% after twelve weeks on diet

compared to their seizure frequency at baseline. This is in line with Barborka's results (16).

5.4. Methodological considerations and limitations

5.4.1 Control group reduces bias and improves the internal validity

We conducted fairly long lasting baseline- and intervention periods in order to reduce seizure variability due to other causes than the intervention. Moreover, implicit in the RCT design is the strength of a control group. Having a control group, corrects for confounders that influence the outcome variable not caused by the intervention. This may imply that a smaller effect is found when comparing controls and intervention groups than other studies applying methods of lower quality. One example in our study was the reduction of seizure frequency in two patients and an increased seizure frequency in two other patients in our control group. This illustrates that spontaneous fluctuations in seizure frequency may occur from one 12-week period to the next, even if no change in treatment has been made.

5.4.2 Other treatments were kept constant during the intervention

Not all previous studies in this field have kept concomitant treatments constant as we did. Rather, in most of these studies adjustments of drugs during the dietary treatment has been the rule more than the exception. Thus, our stringency in this respect was a strength compared to most other studies on this topic.

5.4.3 Patient-reported seizure count is often unreliable

Patient-reported seizure count is inevitably an unreliable measure (194, 195). In a randomised controlled trial addressing this topic by Hoppe et al. (195), as few as 38.5% of patients were able to accurately document their seizures, and 55% of seizures were missed, often due to postictal seizure unawareness. This is a great challenge in all clinical epilepsy-related research where efficacy of a treatment on seizure frequency is the outcome variable. To minimize this source of error, we aimed at including only those who actually were aware of their seizures and able to register them. This was one of our inclusion criteria.

We acknowledge the possibility of error in our patient-reported seizure count. However, if one assume that the error rate is constant during the baseline and intervention periods, in both control and diet group, we believe that our results should be fairly reliable.

5.4.4 Blinding is difficult

Blinding in a dietary intervention is considered difficult. To date, only one randomised, blinded study has been published (196). Both groups were given liquid formula of CKD containing 60 g/day of either glucose or saccharin. Methodologically this study had some serious weaknesses, but it showed that blinding could be possible in a dietary intervention study. A study with minor adjustments to this protocol would be of great interest.

5.4.5 Higher attention, follow-up and care in the diet group may have influenced the results

A disadvantage of not blinding was that the diet group did get higher attention and care than the control group. This may have introduced a bias. For instance, the diet group participants had a follow-up after 4 weeks during the intervention period, while the control group participants did not. To try to compensate for this, we phoned the controls twice during the intervention period and asked for a 3 days' dietary record.

5.4.6 Skewed seizure frequency was a challenge

Compared to those with high seizure frequency, it takes longer time to document a change in the seizure situation among those with low seizure frequency (23). In our data the seizure frequency was highly skewed, and comparing the groups was done using median and $\log_e$ transformation. The heterogeneous seizure frequency may have represented a challenge since the participants with low seizure frequency ideally should have been followed for a longer time. However, with longer baseline and intervention periods, drop-out of the study could have become an even greater challenge.

5.4.7 Small sample size may have entailed a type 2 error

In the RCT we aimed to test if adding modified Atkins diet to current treatment would improve the seizure outcome. The null-hypothesis was that the intervention would reveal no difference between the groups. Details about sample size calculation are stated in Paper 3, page 1570, showing that 35 participants in each group would be sufficient to reject the null hypothesis. When adding 30% for drop-out, a total of 92 participants were to be included, and the study was based on the principle of "intention-to-treat" analysis.

Due to slow participant inclusion, we did not reach 92 participants, but rather stopped at 75, with 28 versus 34 starting the intervention and 24 versus 32 participants completing the intervention, in diet and control groups, respectively.

Too small sample size may give a type 2 error, i.e. when the null hypothesis is retained erroneously. In the intention to treat analysis, we found no effect of the intervention, while among those who completed the intervention we detected a small seizure reducing effect.
We do wonder if the on-treatment-analysis shows a true effect of the dietary treatment. Thus, we speculate that by having had a larger recruitment allowing an intention-to-treat analysis with 35 participants in each group we might have been able to discard the null hypothesis.

5.4.8 Patient selection and generalisability

Our results are generalisable to patients suffering from drug-resistant epilepsy, but not to those with more easy-to-treat epilepsies. Furthermore, we included only patients who were interested in trying the diet, and this is another limitation in generalisability of the results.

During the study period we recognised a group of patients that was slightly cognitively impaired and not able to calculate the dietary regimen, but too well functioning to receive support for calculation and food preparation. This group needs special attention in the future, since dietary treatment is not available to them for the time-being.

5.4.9 Pragmatic versus explanatory design

Our study design was to a large extent pragmatic, meaning that it was conducted in a way that the results should be directly applicable to a clinical situation (197). The other end of the continuum is an explanatory design where the study aims at determining the efficacy of the treatment under ideal conditions. For instance the food could have been premade and supplied free of charge to the participants. Under such conditions, impaired efficacy in some patients due to wrong food calculations or poor compliance would have been largely omitted. Some of those who declined to take part in our study might have accepted to take part under such conditions. However, the resources needed were unavailable to us.

5.5. Ethical considerations

5.5.1 In accordance with the Declaration of Helsinki

The main goal in all clinical research is to avoid harming the patient. This project was executed in accordance with the Declaration of Helsinki. It was approved by the Regional Committee for Medical and Health Research Ethics in South-East of Norway and registered in ClinicalTrials.gov (ID NCT01311440). All participants signed written consent, and the consent document is included in Appendix.

We chose to include some patients with intellectual disability. Without being able to give their consent, this patient group is usually not included in clinical trials. Nevertheless, as some of these patients may have very severe epilepsy, and dietary treatment has proven to be beneficial, we found it unethical to exclude them. The regional ethical committee agreed.

5.5.2 Prevention of serious side-effects

Serious short-term side-effects of dietary treatments have been accounted in some very sick children. One such was cardiomyopathy, possibly due to low selenium status (122). In order to avoid such serious complications, we supplemented the participants with free multivitamin- and minerals and assessed selenium concentration in serum at each follow-up.

Other rare, but serious conditions mentioned in the literature are hepatic failure and pancreatitis. In order to reveal such conditions early, we assessed liver enzymes (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase and alkaline phosphatase) in all participants.

Increased risk of osteopenia and osteoporosis has been documented among children using CKD (100). We assessed calcium intake and vitamin D status in all participants, and supplemented with calcium and vitamin D when necessary.

Another challenge is the presumed increased risk of developing atherosclerosis, documented by elevated LDL-cholesterol (109). In every visit the LDL-cholesterol was assessed, and if elevated, necessary actions were taken; either by dietary advice, cholesterol-lowering medication or termination of the dietary treatment. A large inter-individual variation was found in this respect (109).

We did not detect any lasting negative effects which were not reversed when stopping the 12-week treatment.

5.5.3 Small sample size as an ethical dilemma

To set up an RCT without reaching the anticipated number of participants is an ethical dilemma. It means that resources, not at least patients' efforts were spent on a project from which we were not able to reach a firm conclusion. Fortunately, the resources were not wasted since many patients were able to try the dietary treatment under clinical support, and they expressed gratitude. Besides, we did find some valuable results and thus contributed to the field of research. Retrospectively, we recognise that our original plan was too optimistic, and if we were to do a similar study in the future, the trial should have been set up as a multi-centre study.

5.6. Conclusions

In adults with drug-resistant generalised epilepsy, this work has contributed to increased knowledge of the effect of dietary treatment. Of 13 patients, six completed the intervention of 12 weeks. Four of the six had more than 50% seizure reduction; all four had juvenile myoclonic epilepsy.

In adults with long-lasting drug resistant focal epilepsy, using a pragmatic design, we compared the change in seizure frequency after a 12-week dietary intervention to a control group with no change in treatment. Unfortunately, we had fewer participants than the sample size calculations suggested to be sufficient to detect an effect of the intervention. In spite of this, we detected a small beneficial effect of the diet.

Our results acknowledge the proposals by others, namely that dietary treatment has a place in treating adults with focal drug resistant epilepsy.

During the diet intervention we have detected a reduction of serum concentrations of several AEDs. Thus, a diet-drug interaction should be taken into account in order to achieve an optimal combination of drugs and dietary treatment for individual patients.

5.7. Implications and future perspectives

Some current knowledge gaps and challenges concerning KDT of epilepsy are:

1) Inability to predict who will respond to the treatment

2) Insufficient understanding of mechanisms of action

3) Are there any substances that could enhance the efficacy of dietary treatment in individuals?

4) Lacking knowledge of long-term side-effects

5) Is early initiation of treatment beneficial for efficacy and prognosis?

6) Adherence to KDT is challenging; could the treatment be simplified or even transformed into a pill?

Genetic causes of epilepsy are emerging, and future multi-centre studies that map response to dietary treatment in patients with epileptic encephalopathies caused by single gene mutations would give valuable knowledge. In the years to come, dietary treatment could become part of the long awaited personalised medicine.

In order to utilise KDT better than today, improved understanding of the mechanisms of action is vital. In addition to current animal models, research on epigenetic mechanisms and gut microbiota may give us some answers.

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PAPERS I - IV

I

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ACTA NEUROLOGICA
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Clinical Commentary

Modified Atkins diet may reduce serum concentrations of antiepileptic drugs

Kverneland M, Taubøll E, Selmer KK, Iversen PO, Nakken KO. Modified Atkins diet may reduce serum concentrations of antiepileptic drugs.
Acta Neurol Scand 2015: 131: 187–190.

Background – Modified Atkins diet is a treatment option for patients with pharmacoresistant epilepsy that is not suitable for surgery. In the last few years, we have tried dietary treatment added to antiepileptic drugs (AEDs) in adult patients with severe epilepsy. *Aim of the study* – To examine a possible pharmacokinetic interaction between the modified Atkins diet and AEDs. *Methods* – In four patients, AED serum concentrations were measured before onset and after 4 and 12 weeks on the diet. The patients used combinations of two or three AEDs, including carbamazepine, clobazam, lamotrigine, nitrazepam, oxcarbazepine, valproate, zonisamide, and topiramate. The patients did not change the type or dose of their AEDs during the diet period. *Results* – After 12 weeks on the diet, the average serum concentrations of the respective AEDs were reduced by 35% (range 6–46%) compared to prediet values. *Conclusions* – Modified Atkins diet used as add-on therapy to AEDs in four patients with drug resistant seizures caused a considerable decrease in AED serum concentrations. In individual patients, this could be of clinical relevance, and we recommend that AED serum concentrations should be closely monitored when offering this diet to adults with epilepsy.

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Key words: antiepileptic drugs; refractory epilepsy; ketogenic diet; modified Atkins diet

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Introduction

Most patients with therapy-resistant epilepsy have tried several antiepileptic drugs (AEDs), and the combined use of two or three AEDs is common. In pharmaco-resistant patients, the modified Atkins diet, a less restrictive version of the classic ketogenic diet, may be a treatment option (1). In children, both the modified Atkins diet and the classic ketogenic diet reduce seizure severity and seizure frequency, and they are well tolerated (2).

From 2010, the modified Atkins diet has been offered to adult patients with difficult-to-treat epilepsy at Oslo University Hospital. Since then, we have observed marked reductions in serum concentrations of AEDs in some patients. Here we present details of four cases, with data from follow-ups after 4 and 12 weeks on the diet.

Methods

Dietary treatment

The diet was initiated at home after a brief hospitalization with blood sampling and diet instruction. The intake of carbohydrate was restricted to 16 g/day (3), and high fat intake was encouraged. From diet initiation, one multivitamin tablet (11 vitamins and eight minerals) and 800 mg calcium from pure calcium carbonate were supplemented daily. There were no changes in the AED treatment during the first 12 weeks on diet. Moreover, no other medication was started during the follow-up period.

Assessments

Samples for AED, sodium, and creatinine measurements were collected after an overnight food

and drug fast (12–13 h), while admitted to our hospital. The drugs were administered at 8 pm the day before the assessment. Analyses were performed at Oslo University Hospital, in the same laboratory, using routine assays. Analysis of nitrazepam was not available in our laboratory. The patients and the caretakers were specifically asked whether the prescribed medication could have been skipped at any point. However, they all responded negatively to this question. No intercurrent diseases such as gastroenteritis or fever occurred, which might have influenced the results.

Ketosis was assessed with urine dipstick twice daily, in the morning from the first urine slot and in the evening before the last meal of the day. Body weight was examined after an overnight fast during hospital admission.

Nutrient intakes were calculated using the software program 'Mat på Data' (version 5.0), Norwegian Food Safety Authority, Oslo, Norway based on the Norwegian Food Composition Table of 2006 and were obtained from a 3 days' weighed diet record. A ketogenic ratio is defined as the ratio between total fat (grams) and the sum of carbohydrate (grams) and protein (grams).

Patient cases

Case 1 was an 18-year-old male suffering from focal epilepsy of unknown etiology. He had experienced frequent focal onset seizures from 8 years of age. He was treated with zonisamide 500 mg, carbamazepine 900 mg, and nitrazepam 7.5 mg/day. He lived with his parents and was highly motivated for the diet.

Case 2 was a 25-year-old female with Lennox-Gastaut syndrome and multiple seizure types. Her medication was valproate 600 mg, oxcarbazepine 1500 mg, and zonisamide 600 mg/day. She was living in a residential home with good routines for medicines and strict diet follow-up.

Case 3 was a 47-year-old woman with focal epilepsy caused by multiple intracranial hemangiomas. Her drug treatment consisted of oxcarbazepine 1200 mg and topiramate 550 mg/day.

Case 4 was a 24-year-old male with focal onset seizures of unknown cause. He was treated with lamotrigine 200 mg, clobazam 20 mg, and valproate 1200 mg/day. He was living in a residential home with strict routines for both diet and medication.

Results

After 4 weeks on the modified Atkins diet, all AED serum concentrations were reduced in patient 2 and 4, while in patient 1 and 3, the serum concentrations of carbamazepine and ox-

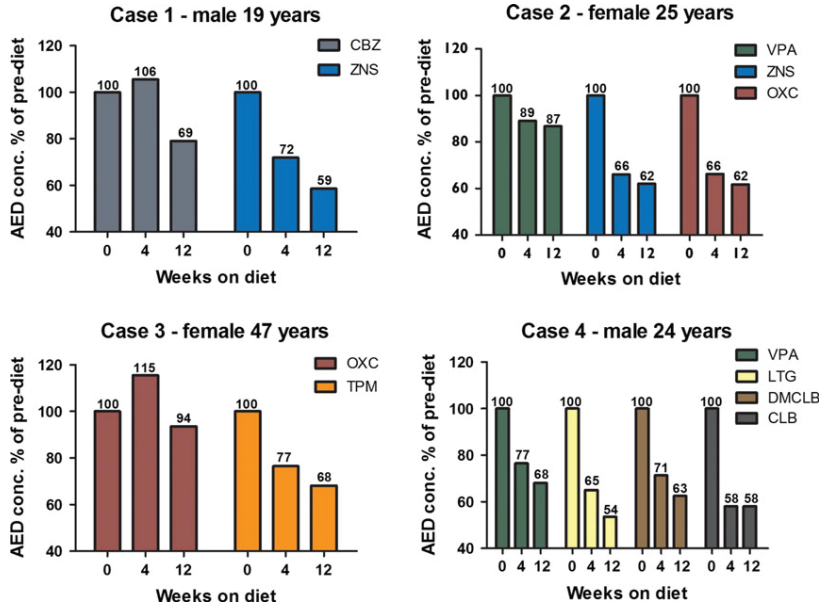

Figure 1. Relative changes in serum drug concentration after 4 and 12 weeks on the modified Atkins diet. The prediet drug concentration was set to 100%. For determinations of oxcarbazepine, we measured 10-hydroxycarbazepine, the active metabolite. The serum concentrations before diet were as follows: Case 1: CBZ 30.1 μmol/l, ZNS 72.7 μmol/l. Case 2: VPA 296 μmol/l, OXC 89 μmol/l, ZNS 140.5 μmol/l. Case 3: OXC 78 μmol/l, TPM 36.1 μmol/l. Case 4: VPA 486 μmol/l, LTG 34.3 μmol/l, DMCLB 1.15 μmol/l, CLB 0.38 μmol/l. CBZ, carbamazepine; CLB, clobazam; DMCLB, desmethyl-clobazam; LTG, lamotrigine; OXC, oxcarbazepine; VPA, valproate; ZNS, zonisamide; TPM, topiramate.

carbazepine, respectively, were increased (Fig. 1). After 12 weeks on the diet, the serum concentrations of all AEDs decreased (range 6–46%). The greatest reduction was observed for lamotrigine in patient 4.

The average daily morning and evening urine ketone concentration during the diet varied between 2.5 and 11.3 mmol/l, indicating a stable ketosis in all four patients. The average ketogenic ratio was 1.7 (range 1.3–1.9), and the energy intake ranged from 1460 to 3365 kcal/day. Energy percentage from fat was on average 78 (range 73–81), from protein 19 (range 15–25) and from carbohydrate 3 (range 2–4), indicating that the patients adhered to the prescribed diet as intended.

Average body weight was reduced by 6.0 kg (range 2.2–8.0 kg), that is from an average of 66.5–60.5 kg after 12 weeks on diet. We found no changes in the serum concentrations of sodium or creatinine.

Discussion

After 4 weeks on the diet, most of the AED serum concentrations were reduced in the four patients. After 12 weeks, the serum concentrations of all AEDs were substantially lowered. To our knowledge, such an interaction between ketogenic diets and AEDs has previously not been reported in adult patients with pharmacoresistant epilepsy.

A Swedish group reported no changes in the plasma concentrations of commonly used AEDs (valproate, lamotrigine, topiramate, clonazepam, and phenobarbital) among 51 children (range 1.3–18 years) with refractory epilepsy after 12 weeks on a ketogenic diet who achieved a ketogenic ratio of 4:1 (n = 39), 3:1 (n = 10) or 2:1 (n = 2) (4). However, the children had their AED doses adjusted during the study period.

In line with our observations, Coppola et al. (5) found a slight, but not statistically significant decrease in the serum concentrations of valproate in 28 children (range 0.5–16 years) on a ketogenic diet (ratio 4:1) after 2 weeks. They claimed that valproate may decrease significantly in some individuals, and if there is an increase in seizure frequency, AED blood concentrations should be measured. There is also published a case on a patient with bipolar disorder treated with valproate who had a relapse of mania while on modified Atkins diet. The authors speculated whether the stimulation of fatty acid transport and metabolism could have lowered plasma levels of valproate (6).

The metabolic response to a comparable diet, namely a low carbohydrate (20 g/day), moderate protein, and high fat (83–85% of calories) diet, was thoroughly examined for 4 weeks in nine lean, healthy males by Phinney et al. (7). As expected, they observed lasting reduced blood glucose, increased blood and urine ketones, and increased free fatty acids. No signs of metabolic acidosis, hypovolemia or change in glomerular filtration rate were detected.

The reasons why the diet causes a drop in AED serum concentrations are not known. Theoretically, the diet may influence drug absorption, distribution, metabolism and excretion.

Absorption

In general, drug absorption in the intestine may be influenced by food intake. However, AEDs are lipophilic substances, and those used by our patients, except for carbamazepine, will be absorbed almost 100%, regardless of concurrent meals. Although there is a lack of conclusive evidence, studies indicate that a high fat diet may increase AED absorption rather than decrease it (8, 9). Thus, it seems unlikely that our findings can be explained by diet-induced altered drug absorption.

Volume of distribution

Our four patients experienced on average 10% weight reduction during the diet period. This reduction would expectedly give an increase in AED concentration. Thus, the weight reduction is less likely to be the explanation of our observations. However, AEDs are protein-bound to a variable extent, and fluctuations in serum albumin as a consequence of negative energy balance might transiently influence AED protein binding, which again could affect the serum concentration of AEDs.

Metabolism

To a large extent, the body adjusts to the new fuel situation during the first 4 weeks (7). The drugs used by our four patients are all metabolized in the liver, although to varying degrees (10). Knowing that the modified Atkins diet implies doubling or tripling of the dietary fat content compared to a normal diet, it is possible that the diet imposes a drug – fat interaction in a similar manner as the well-known drug – drug interaction between AEDs and numerous other drugs (11). For the metabolism of many AEDs, cytochrome p450 enzymes (CYP) are essential, but these enzymes also play a decisive role in the

hepatic fat metabolism. The CYPs, once believed to mainly deal with detoxification, are found to execute numerous endogenous functions (11), such as synthesis and/or breakdown of eicosanoids, steroids, cholesterols, and bile acids, all highly relevant for the lipid homoeostasis. The liver uridine glucuronyl transferases (UGTs) are enzymes involved in metabolism of AEDs. These may also be influenced by the increase in fat turnover imposed by the diet. Thus, the reductions in AED serum concentration in our patients may be explained by diet-associated induction of CYPs, UGTs and/or other drug metabolizing enzymes due to a very high dietary fat intake.

Excretion

During starvation, large amounts of non-esterified fatty acids and ketone bodies impose a weak metabolic acidosis, and lowered blood- and urine pH is frequently seen among children on the ketogenic diet. Excretion and serum concentration of phenobarbital, an old AED, are sensitive for acid-base variations in the urine, and alkalinization of the urine results in increased drug excretion. Whether this phenomenon may apply to the relevant AEDs in this study is, to our knowledge, not documented.

Conclusion

Based on the results from our four patients, we claim that AED serum concentrations can be substantially reduced among adults treated with the modified Atkins diet. Hence, our observations are of putative clinical importance as lowered serum concentrations of AEDs are expected to increase seizure susceptibility, and we recommend that AED serum concentrations should be closely monitored when offering dietary treatment to adults with epilepsy.

Due to the limited number of patients, we are cautious about generalizing our findings to a wider population of intractable epilepsy. However, our case report provides 'proof of principle' that this can occur at least in some patients.

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The research and the manuscript drafting were carried out by MK. All authors designed the research and contributed to writing the paper. All authors read and approved the final manuscript.

Conflict of interest

None of the authors have any conflict of interest to disclose. We confirm that we have read the position of the Journal on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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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 fingerprick 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 nonparametric 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.

Table 1
Patient characteristics and effect of the diet on seizures and on quality of life.

Patient/gender/age	Diagnosis	Age at epilepsy onset (years)	# of previous AEDs	Current AEDs	Seizure types	Diet duration (weeks/days)	Mean weekly seizure frequency at baseline (range)	% change in mean weekly seizure frequency in W1–4/W5–12	Change in seizure severity scores W12	Change in quality-of-life scores W12	Reason for continuing or terminating diet
1/F/38	JME	14	7	CLB, LTG, VPA	GTC, MC, A	23/6	0.8 (0–2)	+20/+5	0	4	Lack of efficacy
2/F/58	JME	7	5	LEV	GTC, MC, A	26/1	9.7 (3–16)	−53/−53	−5	3	Responder, not enough efficacy
3/F/16	Jeavons	9	6	LEV	MC (eyelid), A	2/6	24 (20–28)	NA	NA	NA	Lack of motivation
4/F/38	JME	14	2	LEV	MC	42/6	17.5 (5–28)	−39/−9	−2.5	2	Not enough efficacy
5/F/36	JME	15	6	None	GTC, A	0	NA	NA	NA	NA	Lack of motivation
6/F/18	JME	5	3	None	GTC, MC, A	4/1	352 (124–636)	−48/NA	NA	NA	Lack of motivation
7/F/23	JME	13	1	VPA, LEV, CLB	GTC, MC	9/2	NA	NA	−5	−5	Excluded, poor compliance
8/F/46	JME	13	6	PHT	GTC, MC	132/6	0.8 (0–3)	+50/−55	−70	23	Responder, still on diet
9/F/40	JME	10	6	TPM, LTG	GTC, MC, A	73/6	81 (61–108)	−66/−95	−57.5	23	Responder, still on diet
10/F/53	CAE	1	12	CLB, ESM, ZNS	GTC, A	4/1	0.9 (0–2)	−18/NA	NA	NA	Lack of motivation
11/M/32	Unknown	0	6	PB, CLB, VPA	GTC, T, AT	8/4	28.3 (21–38)	+72/NA	NA	NA	Seizure aggravation
12/F/30	CAE	2	5	ZNS	GTC, A	10/5	11.9 (0–100)	NA	NA	NA	Excluded, changed AED dose
13/F/47	JME	19	9	OXC, LEV, TPM	GTC, MC, A	21/6	25.7 (6–64)	−82/−52	−1	21	Responder, still on diet

Abbreviations: W = week, F = female, M = male, CLB = clobazam, CZP = clonazepam, ESM = ethosuximide, LTG = lamotrigine, VPA = valproate, LEV = levetiracetam, PHT = phenytoin, TPM = topiramate, PB = phenobarbital, ZNS = zonisamide, GTC = generalized tonic–clonic, MC = myoclonic, A = absence, T = tonic, AT = atonic, JME = juvenile myoclonic epilepsy, CAE = childhood absence epilepsy.

3.3. Changes in AED serum concentrations

Of the six participants who completed 12 weeks on diet, the three who used one AED had an increase in mean serum concentrations of 29 (range: 27–30) %. The three patients who used more than one AED experienced a reduction in mean serum concentrations of 19 (range: 8–28) %.

3.4. Tolerability

Among those who completed the intervention, mean weight reduction after 12 weeks on the diet was 6.5 (range: 4.3–8.1) kg. One patient experienced symptoms of gallstones when tapering off the diet after 10 months.

3.5. Metabolic changes

After 12 weeks on the diet, median free carnitine concentration was reduced by 11 (−31 to −3, $p = 0.028$) μmol/l whereas median total carnitine concentration was reduced by 5 (−24 to −1, $p = 0.027$) μmol/l. Median HbA1c decreased by 0.35 (−0.6 to −0.1, $p = 0.027$) %. The median LDL cholesterol concentration increased by 0.45 (0.00–0.70, $p = 0.042$) mmol/l, while the median number of thrombocytes was reduced by 32×10^9/l (−83 to −10, $p = 0.028$).

4. Discussion

4.1. Main findings

In this study of patients with drug-resistant generalized epilepsy, four of the thirteen participants (31%) achieved >50% seizure reduction, which is in accordance with recent reviews [1,2]. Six of the thirteen (46%) patients, all diagnosed with JME, completed the 12-week diet period. Of those six, four (67%) were responders. A considerable improvement in health-related quality of life characterized three of the four responders [12]. They all chose to continue the treatment. In two of the three, seizure severity was also remarkably reduced.

4.2. Reasons for drop-out

Seven of thirteen (54%) did not complete the study period. Reasons for discontinuing the study are listed in Table 1. One participant had a 72% seizure increase after 4 weeks. Notably, in this case, the serum concentration of AEDs dropped 24–44%, and this may be the explanation for the aggravation.

Older participants succeeded more often than the younger ones in adhering to the diet. As a general impression, they had more regular daily routines, which possibly could have facilitated meal planning and, thus, improved adherence to the diet.

Unquestionably, this restrictive diet requires the ability to calculate, plan, and stay focused. The neuropsychological profile associated with JME may impose an additional challenge on these patients to comply with the diet [13].

4.3. Female predominance

The female predominance in the study could be related to the fact that JME occurs more frequently in women than in men. A female to male ratio of 2.8:1 has been reported [14]. In a cohort of children with idiopathic generalized epilepsy, the girls to boys ratio was 3.6:1 [15]. Moreover, one might speculate that women could be more interested in dieting and using food as a remedy, and thus, such a treatment may have a greater appeal among females than males. Patients worried about side effects of valproate (weight increase and teratogenicity) may also find the diet appealing.

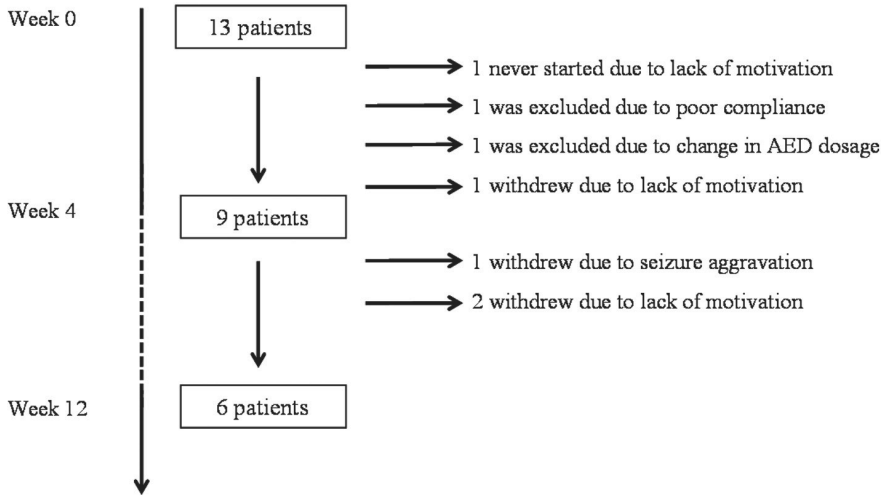

Fig. 1. Number of patients attending the follow-ups and reasons for withdrawal from the study.

4.4. Tolerability

Fluctuation in fat intake while starting or ending the diet may increase the risk of gallstones in susceptible individuals. Apart from the case with gallstones and the participant who experienced seizure aggravation, the diet was well-tolerated.

For most participants, weight loss was favorable. All six participants who completed the study achieved ketosis. Also, the serum concentration of free and total carnitine dropped significantly. However, symptoms of carnitine depletion such as muscle weakness and extreme tiredness were not reported. None of the participants were diabetic. The reduction in HbA1c indicates a lowered postprandial level of blood glucose over 12 weeks on diet. The serum concentration of LDL cholesterol increased, as reported earlier [1]. Due to elevated LDL cholesterol, for individuals who continue the diet over a prolonged period, the risk of cardiovascular disease may increase. Dietary recommendations to increase unsaturated fat and reduce saturated fat will, thus, be important [16,17]. A small and probably clinically insignificant reduction in thrombocyte count was observed. To our knowledge, such a change has not been reported earlier.

4.5. Previous work

Groomes et al. reviewed the efficacy of dietary treatment among 154 children and adolescents with medically refractory childhood and juvenile absence epilepsies [18]. Among these, 69–82% were responders, and 19–34% achieved seizure freedom. Nei et al. [19] reported one patient with absence epilepsy experiencing considerable seizure reduction. Thammongkol et al. [20] reported good response in three patients with genetic generalized epilepsy, one of them being an adult with JME. Moreover, Kossoff et al. retrospectively reviewed eight adolescents and adults with JME, of whom 5 responded to the modified Atkins diet after 3 months [7].

4.6. Influence of the diet on AED serum concentrations

The serum concentrations of AEDs seemed to be influenced by the diet. An increase of the serum concentrations was observed among those on monotherapy, whereas a reduction was noted among those on polytherapy. We recently reported a reduction in AED serum concentrations on polytherapy in four patients treated with the modified Atkins diet, and speculated whether this reduction could be due to an interaction between AEDs and the high fat component of the diet [21]. However, due to the small number of participants, wide variety of AEDs, and multiple combinations of AEDs in use, no conclusions can yet be drawn. However, we believe that serum concentrations should be followed during dietary treatment, as a reduction in serum concentration could be a cause of seizure aggravation.

4.7. Clinical implications

Response to the diet may occur within days or a few weeks. However, one patient experienced a transient seizure aggravation during the initial 2–3 weeks on diet, after which she became seizure-free. We, therefore, suggest that the patients should stay on the diet for 3 months before any conclusion is drawn, especially in those with less than weekly seizures. This is longer than what was suggested by Kossoff et al. [11] who suggested that 2 months of trial time on the diet would be sufficient to detect an improvement.

The retention rate was 23%, which is somewhat higher than the very low long-term adherence reported by Klein et al. [1]. This could, at least partly, be due to the hospital admission before starting the diet, which is not a normal practice elsewhere. Furthermore, the three participants who continued the diet claimed that this was the most effective treatment they had ever tried. Thus, in our opinion, the modified Atkins diet should be considered a treatment option also for adults with difficult-to-treat epilepsy. However, a major challenge is to support the patients to adhere to the diet over time. This may be accomplished by improved recipes, cooking classes, inspiration letters, and group meetings, in addition to regular follow-up.

4.8. Limitations of the study

Limitations to this study include few participants, no control group, and an open label design. However, the study was executed in a pragmatic way relevant to the clinical treatment of drug-resistant epilepsy.

4.9. Future work

In this open prospective study, we have shown that some adult patients with JME respond to the modified Atkins diet. More research, preferably with randomized controlled trials comparing recommended antiepileptic drug therapy with the diet, are needed to document the long-term response, retention rate, and adverse effects of the diet. For those whose seizures failed to improve with two or more drugs and who are motivated to try this demanding treatment, health-care professionals' efforts should be directed to support them.

5. Conclusion

Of six adults with pharmacoresistant JME who completed 12 weeks of treatment with the modified Atkins diet, four responded well. Of these, three have continued the treatment. For some patients with drug-resistant genetic generalized epilepsy, such a diet may be a worthwhile treatment option. However, a prerequisite for success is that the patient is highly motivated and receives adequate follow-up.

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IV

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

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SUMMARY

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 a 12-week dietary treatment as add-on to AEDs is 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*, estimated.

Results: Mean age of patients was 37 years (16-65). Mean serum concentrations of carbamazepine, clobazam, and valproate were significantly reduced after 4 and 12 weeks of the diet period ($<0.001 \leq p \leq 0.02$). Lacosamide, lamotrigine and topiramate were less reduced ($0.02 \leq p \leq 0.08$), while the serum concentrations of oxcarbazepine, zonisamide and levetiracetam were unchanged ($0.06 \leq p \leq 0.90$). 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 were -10.5 % (95% CI -14.1 to -6.8; n=60; $p<0.001$) and -13.5% (95% CI -18.8 to -8.3; n=56; $p<0.001$), respectively. Percent change in serum concentration of AEDs was not significantly correlated to percent change in seizure frequency after 12 weeks of dietary treatment ($r=0.14$, $p=0.33$, n=53) but negatively correlated to urine ketosis ($r=-0.43$; $p=0.003$; n=46).

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

1 INTRODUCTION

The ketogenic diets, including a variant of the diet called 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 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] Interestingly, we discovered a reduction in serum concentration of clobazam and carbamazepine, and this might have influenced the results. Also, in a case report we presented four adults with a marked reduction of AED serum concentrations after initiation of modified Atkins diet,[4] suggesting that there may be a pharmacokinetic interaction between AEDs and the diet. To our knowledge, this has not previously been studied in adults.

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

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 were 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 signed by 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 into the study. The inclusion scheme is given in figure 1. Screening and inclusion was performed by a senior neurologist (KON or EM) and a clinical nutritionist (MK).

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; 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 non-epileptic 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 four 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 one-day hospital admissions 4 and 12 weeks after initiation of the diet.

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 after an 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 including the baseline visit. 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 1 or 2 participants.

To assess diet adherence, participants recorded urine ketosis twice daily during the 12 weeks on diet using urine dipsticks (Ketostix, Bayer Healthcare, Leverkusen, Germany). From these recordings, mean 12-week morning and evening urine ketosis was calculated. Also, 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, while the evening sample was collected immediately before the last meal of the day. Also, the blood concentration of glucose and 3-hydroxybutyrate was assessed twice (morning and evening) based on a finger-prick blood sample using ABBOTT Freestyle Optium Blood Glucose Test Strips and Precision Xtra Blood Ketone Test Strips (Abbott, Alameda, CA, USA), 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 three 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 proportion of patients who were seizure free, had >90%, >50% and >25% seizure reduction or who experienced seizure aggravation, after 12 weeks on the diet compared to the baseline period, average daily intake of energy and macro-nutrients, 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 week 5 to 12 in the diet period.

2.5 Statistical analysis

Data are presented as mean (range or 95% confidence interval [CI]), or frequency. As for the primary outcome, serum concentrations of drugs after 4 and 12 weeks of diet period were

compared to baseline using paired t-test. Also, paired t-test was used to compare the serum concentrations at 4 and 12 weeks of treatment. One-sample t-test was used to test mean percent change. 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, >90%, >50% and >25% seizure reduction were calculated as mean weekly seizure frequency from baseline to weeks 5-12 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. Further, between percent change in serum concentration of AEDs and weight change, and between per cent 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, Armonk, NY, USA) was used for the statistical analyses.

3 RESULTS

Baseline demographic and clinical characteristics of the 63 participants are presented in Table 1A. Dietary intake of energy, fat, protein and carbohydrate after 4 and 12 weeks on diet is presented in Table 1B.

AED use was as follows: 20 used one drug, 21 used two, 19 used three, and two 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. The 4-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 ($5 \leq n \leq 19$) diet intervention, except for LEV (Table 2 and Supplemental 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 were -10.5% (95% CI -14.1 to -6.8; n=60; p<0.001) and -13.5% (95% CI -18.8 to -8.3; n=56; p<0.001), 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<0.001) and -13.7% (95% CI -19.4 to -8.0; n=47; p<0.001) 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, i.e. 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=0.21). The distributions of AEDs were similar to those in the main analyses.

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=0.03) and -12% (95% CI -25 to 1; n=17; p=0.06), respectively. When excluding three subjects who used LEV, the mean percent reduction was -8% (95% CI -13 to -2; n=17; p=0.02) and -18% (95% CI -30 to -6; n=15; p=0.006) 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 while 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% to +278% (i.e. 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 ten patients using CLB who completed 4 weeks on diet, three had a prominent seizure increase, three responded with a reduction in seizure frequency, while the rest remained unchanged.

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

seizure frequency. Five (9%) participants 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 = 0.14, p = 0.331, n = 53). This estimate was similar after exclusion of the four participants who experienced >90% seizure exacerbation (r = 0.12, p = 0.41, n = 49). Excluding those using LEV (n=16) gave similar results (r = 0.17, p = 0.32, n = 37).

Mean body 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' treatment was -2.4 kg (95% CI; -3.2 to -1.7; n=56; p<0.001) and -4.5 kg (95% CI; -3.3 to -5.8; n=54; p<0.001), respectively. We found no significant correlation between weight change and percent change in serum concentration of AEDs after 12 weeks of treatment (r = -0.02, p = 0.89, n = 50). Neither did we find any correlation between dietary ketogenic ratio and ketosis (r= 0.16; p=0.30; 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 Supplemental Figure S2. Ketosis increased significantly from diet start to week 4 (p<0.001) and from diet start to week 12 (p<0.001). Also, there was a decrease from week 4 to 12 which was statistically significant for urine ketosis measured in morning and evening and blood ketosis measured in evening (0.006<p<0.009) but not for blood ketosis measured in the morning (p=0.14) (Table 2 and Supplemental Figure S2 A-D). Blood glucose assessed morning and evening in ward and at the laboratory in venous blood were significantly reduced from baseline to week 4 on the diet (p<0.001), and then increased to week 12 (p=0.35 for

morning, p=0.02 for evening and p=0.03 in venous blood) (Table 2 and Supplemental Figure S2 E-G), but not up to the mean level at baseline. HbA1c values decreased significantly from baseline to 4 and 12 weeks ($p<0.001$) (Table 2 and Supplemental 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 Supplemental Table S1. Scatter plots of the variables are shown in Supplemental Figures S3A-C, illustrating how the per cent change in AED serum concentrations (excluding LEV) correlates 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 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, while 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 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. 1) Those 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. 2) 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 non-interventional 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, non-adherence 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 lipofilic 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 high-dose iron supplement may reduce absorption of CBZ in elderly.[11] We therefore cannot rule out that there might have been specific, so far undetermined, dietary substances introduced by the diet having a similar effect on our patients..

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, 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 between diet and control group.[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 up-regulate several cytochrome P450 enzymes that metabolize several AEDs.[13] Their metabolism may be speeded up as a result of the high fat intake, while LEV, which is not metabolized in the liver, showed no reduction in serum concentration.[14] 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, while 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.

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 week 4 and 12 on the diet. This may reflect an adaption taking into account transcriptional up-regulation of enzymes of ketogenic pathways that must be assumed during 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.[15] Alternatively, drug doses could be increased to compensate for the diet-induced drop.

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] Also, 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 existing regimen of AEDs is to achieve an additive or synergistic seizure-reducing effect. Unfortunately, perhaps due to 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 ketogenic diet.[16] However, there are several major methodological differences between our study and the Swedish study making a comparison difficult. 1) There may be differences in drug metabolism between children and adults. 2) Dahlin et al. changed the drug doses in many children immediately before diet start and also during the dietary treatment. Moreover, 3) many children in the study by Dahlin et al. had a considerable weight reduction. 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 non-significant reduction of serum concentration of VPA after 30 days on diet.[17] Heo et al. retrospectively studied 139 children for at least 30 days on various ketogenic diets and observed a significant reduction in serum concentration of VPA.[12] Moreover, Heo et al. observed non-significant reduction of CBZ, LTG, LEV and TPM, possibly due to a different study design than ours.

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 may counteract a seizure-reducing effect of

ketogenic diets. Thus, we recommend monitoring of the serum concentrations of the adjunctive AEDs in patients treated with such diets.

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DISCLOSURE

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.

KEY POINTS

- This trial examined the influence of modified Atkins diet on serum concentration of concomitant antiepileptic drugs in adults in with refractory 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, while the concentrations of levetiracetam were unchanged
- We found a significant negative correlation between the reduction in AED serum concentrations and the extent of ketosis

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

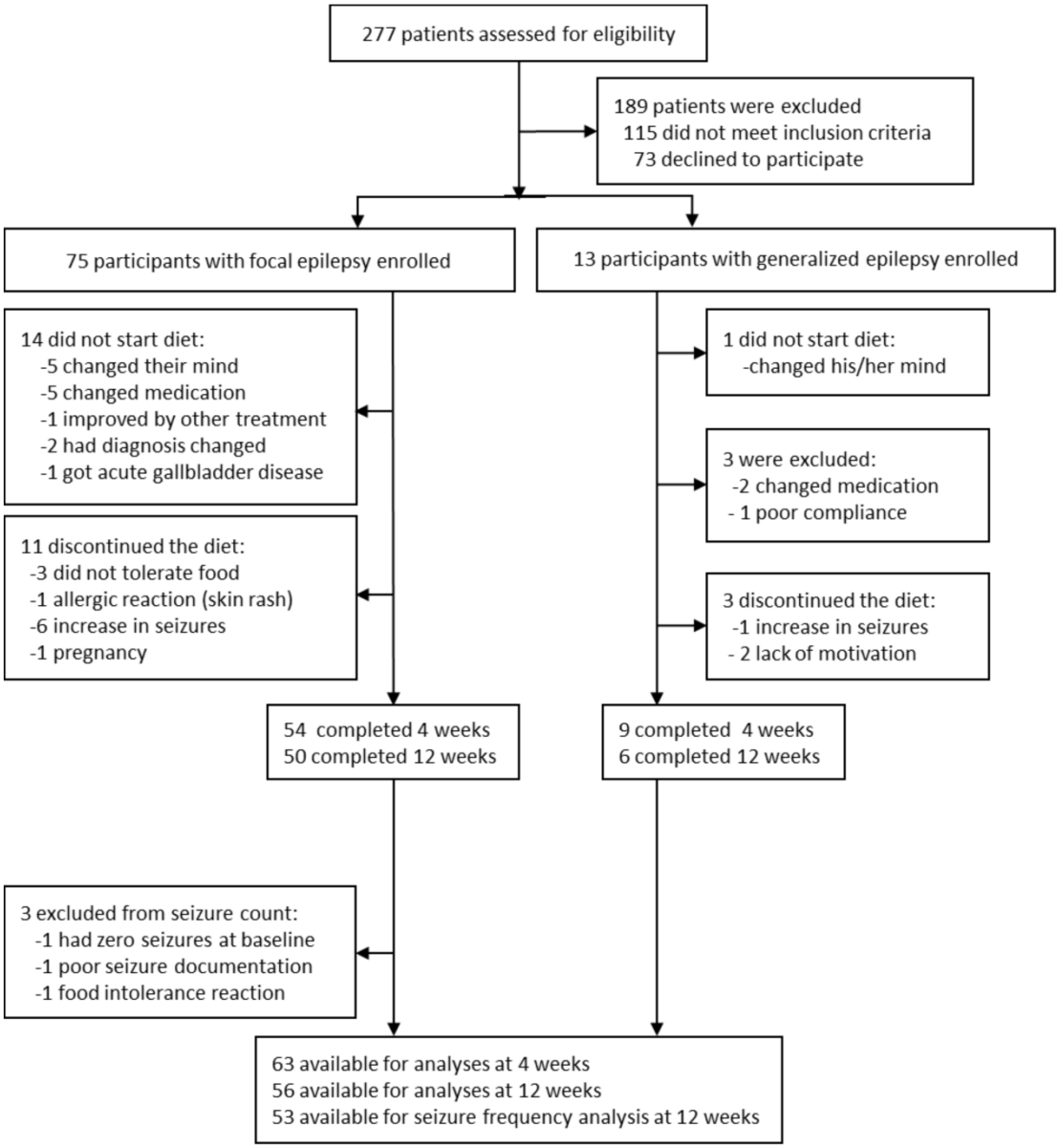

TABLE 1 A: Baseline characteristics of the 63 participants. B: Daily dietary intake after 4 and 12 weeks on modified Atkins diet given as total energy and energy percent (E%) from fat, protein and carbohydrate, and the intake of fat, protein and carbohydrate in grams.

A.

Age (years)	37 (16 – 65) [1]
Female sex	40 (60%)
Epilepsy etiology	
Structural	16 (25%)
Genetic	8 (13%)
Infectious	4 (6%)
Unknown	35 (56%)
Age at first seizure (years)	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 weeks on diet (n=54) [2]	12 weeks on diet (n=47) [2]
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)

AEDs = Antiepileptic drugs

[1] Data are mean (range) or frequency (%)

[2] Values presented as mean (95% confidence interval)

FIGURE 2: Percent change of all AED serum concentrations taken together (mean 95% CI) after 4 and 12 weeks on the diet compared to no change, test value zero is indicated by the dotted line. ** p <0.001 (significant)

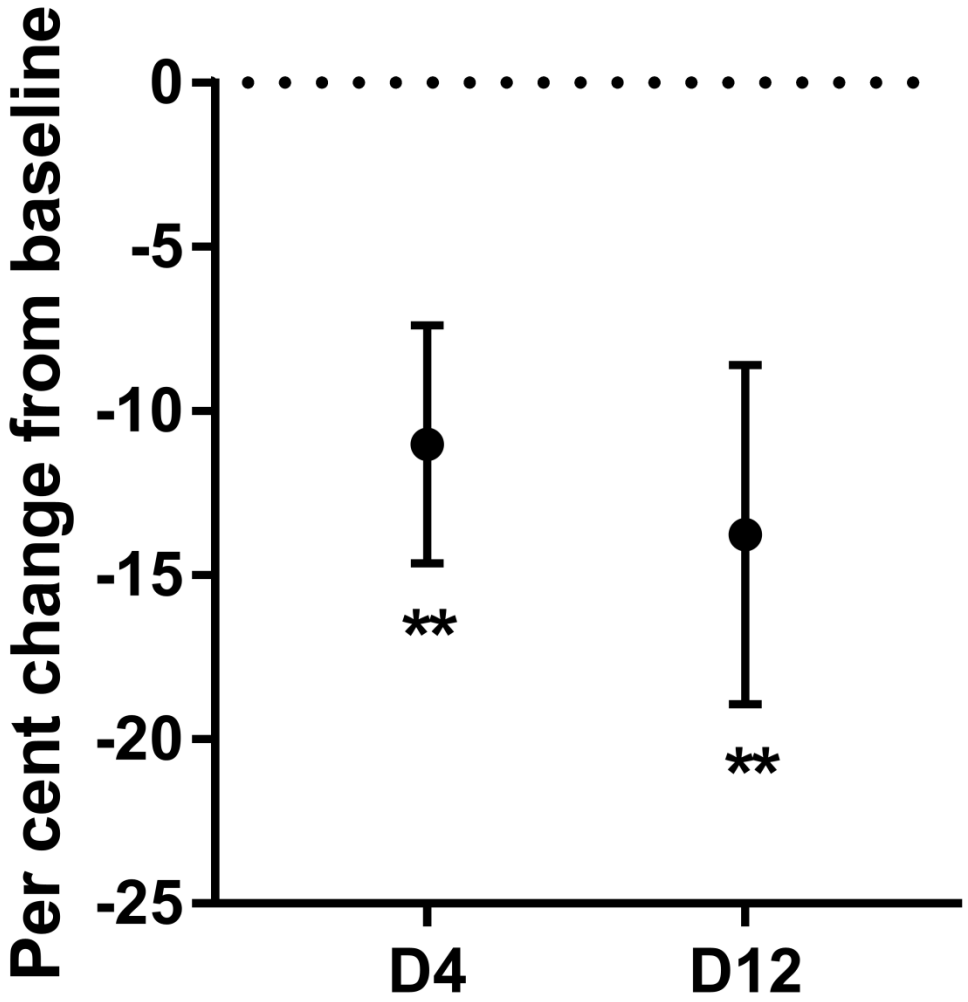

TABLE 2: Change in serum concentrations of antiepileptic drugs, ketosis and glucose after 4 and 12 weeks treatment with modified Atkins diet.

	Before diet start	**4 weeks on diet**		**12 weeks on diet**		**4 vs 12 weeks**
Serum concentration	**n mean (95% CI)**	**change from baseline n mean (95% CI)**	**p[1]**	**change from baseline n mean (95% CI)**	**p[2]**	**p[3]**
CBZ, µmol/L	n=8 36.8 (32.6-41.0)	n=8 -4.9 (-8.7--1.0)	0.02	n=7 -8.5 (-12.7--4.2)	0.003	0.10
CLB, µmol/L[4]	n=10 4.4 (2.3-6.4)	n=10 -1.1 (-1.8--0.4)	0.007	n=9 -1.5 (-2.6--0.5)	0.009	0.08
CZP, nmol/L	n=2 47.0 (-232.5-326.5)	n=2 -1.0 (-26.4-24.4)		n=2 -7.5 (-26.6-11.6)		
LCM, µmol/L	n=6 16.7 (10.8-22.6)	n=6 -1.5 (-3.2-0.2)	0.08	n=6 -2.5 (-4.3--0.7)	0.02	0.40
LEV, µmol/L	n=16 81.6 (58.6-104.8)	n=14 0.6 (-9.7-11.0)	0.90	n=16 3.5 (-5.7-12.7)	0.43	0.91
LTG, µmol/L	n=15 27.7 (21.3-34.2)	n=14 -3.4 (-5.7--1.2)	0.006	n=15 -3.2 (-6.9-0.5)	0.09	0.61
OXC[5], µmol/L	n=19 81.5 (68.9-94.1)	n=19 -2.8 (-9.0-3.4)	0.35	n=17 -7.1 (-14.4-0.2)	0.06	0.07
PB, µmol/L	n=3 50.3 (-41.8-142.5)	n=3 -8.0 (-36.0-20.0)		n=2 -11.0 (-138.1-116.1)		
PGB, µmol/L	n=2 18 (18-18)	n=2 1.5 (-43.0-46.0)		n=2 4.5 (-1.9-10.9)		
PHT, µmol/L	n=4 42.5 (30.4-54.6)	n=3 -10 (-27.2-7.2)		n=4 -8.3 (-30.3-13.8)		
TPM, µmol/L	n=10 24.4 (19.6-29.2)	n=10 -3.5 (-7.6-0.6)	0.08	n=9 -4.0 (-7.3--0.6)	0.03	0.95
VPA, µmol/L	n=16 489 (403-576)	n=16 -85 (-127--44)	0.001	n=15 -100 (-142--59)	<0.001	0.15
ZNS, µmol/L	n=5 78.0 (31.8-124.4)	n=5 -18.4 (-41.0-4.2)	0.09	n=4 -28.1 (-58.3-2.1)	0.06	0.06
All drugs[6] % change	---	n=60 -10.5 (-14.1--6.8)	<0.001	n=56 -13.5 (-18.8--8.3)	<0.001	0.10
Ketosis[6] mmol/L	**n mean (95% CI)**	**n mean (95% CI)**	**p[1]**	**n mean (95% CI)**	**p[2]**	**p[3]**
Urine, morning[7]	n=51 0.1 (-0.1-0.3)	n=48 4.3 (3.2-5.5)	<0.001	n=46 2.9 (1.9-3.8)	<0.001	0.006
Urine, evening[7]	n=50 0.1 (-0.0-0.1)	n=46 5.3 (4.1-6.6)	<0.001	n=45 3.2 (2.1-4.3)	<0.001	0.009
Blood, morning[8]	n=52 0.2 (0.1-0.3)	n=52 1.4 (1.1-1.8)	<0.001	n=49 1.1 (0.8-1.4)	<0.001	0.14
Blood, evening[8]	n=52 0.1 (0.1-0.2)	n=50 1.5 (1.1-1.8)	<0.001	n=48 0.9 (0.6-1.2)	<0.001	0.006
Urine daily morning[7,9]	---	n=50 4.7 (3.6-5.8)	---	n=47 4.4 (3.3-5.6)	---	---
Urine daily evening[7,9]	---	n=50 6.0 (4.9-7.1)	---	n=47 5.7 (4.5-6.9)	---	---
3-hydroxy butyrate[10,12]	n=25[9] 0.1 (0.0-0.1)	n=27 1.2 (0.9-1.5)	<0.001	n=28 0.8 (0.5-1.1)	<0.001	0.02

Glucose mmol/L	n mean (95% CI)	n mean (95% CI)	p[1]	n mean (95% CI)	p[2]	p[3]
Morning[11]	n=55 5.1 (4.9-5.3)	n=53 4.5 (4.3-4.7)	<0.001	n=52 5.0 (4.8-5.1)	0.35	<0.001
Evening[11]	n=53 5.3 (5.0-5.6)	n=51 4.5 (4.3-4.8)	<0.001	n=48 4.8 (4.6-5.2)	0.02	0.06
Morning[12]	n=62 5.1 (5.0-5.3)	n=60 4.8 (4.7-5.0)	<0.001	n=56 5.0 (4.9-5.1)	0.03	0.001
HbA1c[12], %	n=63 5.3 (5.2-5.4)	n=59 5.1 (5.0-5.2)	<0.001	n=57 5.0 (4.9-5.1)	<0.001	0.006

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

[1]Comparing values at baseline and 4 weeks of treatment using paired t-test

[2] Comparing values at baseline and 12 weeks of treatment using paired t-test

[3] Comparing change from baseline to 4 weeks with change from baseline to 12 weeks using paired t-test

[4] Desmethylclobazam, a metabolite

[5] Eslicarbazepine is analyzed as OXC (licarbazepine)

[6] Variation in n is due to missing values

[7] Using urine dipsticks, Ketostix

[8] Using Precision Xtra Blood Ketone Test Strips

[9] Morning and evening urine ketosis during 4 and 12 weeks assessed by patients or caregivers

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

[11] Using Blood Glucose Test Strips

[12] Laboratory assessments

LEGENDS OF SUPPLEMENTAL TABLES AND FIGURES

FIGURE S1: Mean (95% CI) serum concentrations of AEDs (µmol/L) at baseline (left Y-axis) and difference from baseline after 4 and 12 weeks (right Y-axis) of treatment with modified Atkins diet. Paired t-test was used to compare values at 4 and 12 weeks versus baseline: * $0.001 \leq p < 0.05$; ** $p < 0.001$.

CBZ=carbamazepine, CLB= clobazam, LCM=lacosamide, LEV=levetiracetam, LTG=lamotrigine, OXC=oxcarbazepine, TPM=topiramate, VPA=valproate, ZNS=zonisamide

FIGURE S2: Mean (95% CI) of levels of ketosis and glucose at baseline and after 4 and 12 weeks of treatment with modified Atkins diet. A) Morning urine ketosis; B) Evening urine ketosis; C) Morning blood ketosis; D) Evening blood ketosis; E) Morning blood glucose; F) Evening blood glucose; G) Venous fasting glucose; H) HbA1c. Paired t-test was used to compare values at 4 and 12 weeks versus baseline, and at 12 weeks versus 4 weeks: * $0.001 \leq p < 0.05$; ** $p < 0.001$.

TABLE S1: Spearman’s correlation between per cent change in serum concentration of all AEDs (excluding LEV) and ketosis, both measured in the morning and evening, in urine and in blood, after four and twelve weeks of treatment, self-assessed at home and during admission. Fasting glucose and HbA1c was assessed in venous blood

FIGURE S3A Scatter plot of per cent change in AED serum concentrations (excluding LEV) and ketosis, morning and evening, in urine and in blood, after four and twelve weeks of treatment, during admission. Blood ketose was assessed by finger-prick in ward during admission. A. Morning urine ketosis. B. Evening urine ketosis. C. Morning blood ketosis. D. Evening blood ketosis

FIGURE S3B Scatter plot of per cent change in AED serum concentrations (excluding LEV) and self-assessed urine ketosis, using urine dipsticks measured in the (A) morning and (B) evening daily during 12 weeks on diet, mean values calculated after four and twelve weeks of treatment

FIGURE S3C Scatter plot of per cent change in AED serum concentrations (excluding LEV) and blood glucose/HbA1c, both measured in the morning and evening, after four and twelve weeks of treatment, during admission. Morning/evening glucose was assessed in finger-prick and measured in ward during admission, while fasting glucose and HemoglobinA1c was assessed in venous blood and analyzed in laboratory. A. Morning glucose B. Evening glucose. C. Venous sample fasting glucose D. Hemoglobin A1c

Supplemental Material

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

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[f]Department of Research and Development, Division of Clinical Neuroscience, Oslo University Hospital and the University of Oslo, Oslo, Norway

FIGURE S1: Mean (95% CI) serum concentrations of AEDs (µmol/L) at baseline (left Y-axis) and difference from baseline after 4 and 12 weeks (right Y-axis) of treatment with modified Atkins diet. Paired t-test was used to compare values at 4 and 12 weeks versus baseline: * $0.001 \leq p < 0.05$; ** $p < 0.001$. Details, including sample sizes, are given in Supplemental Table S1.

CBZ=carbamazepine, CLB= clobazam, LCM=lacosamide, LEV=levetiracetam, LTG=lamotrigine, OXC=oxcarbazepine, TPM=topiramate, VPA=valproate, ZNS=zonisamide

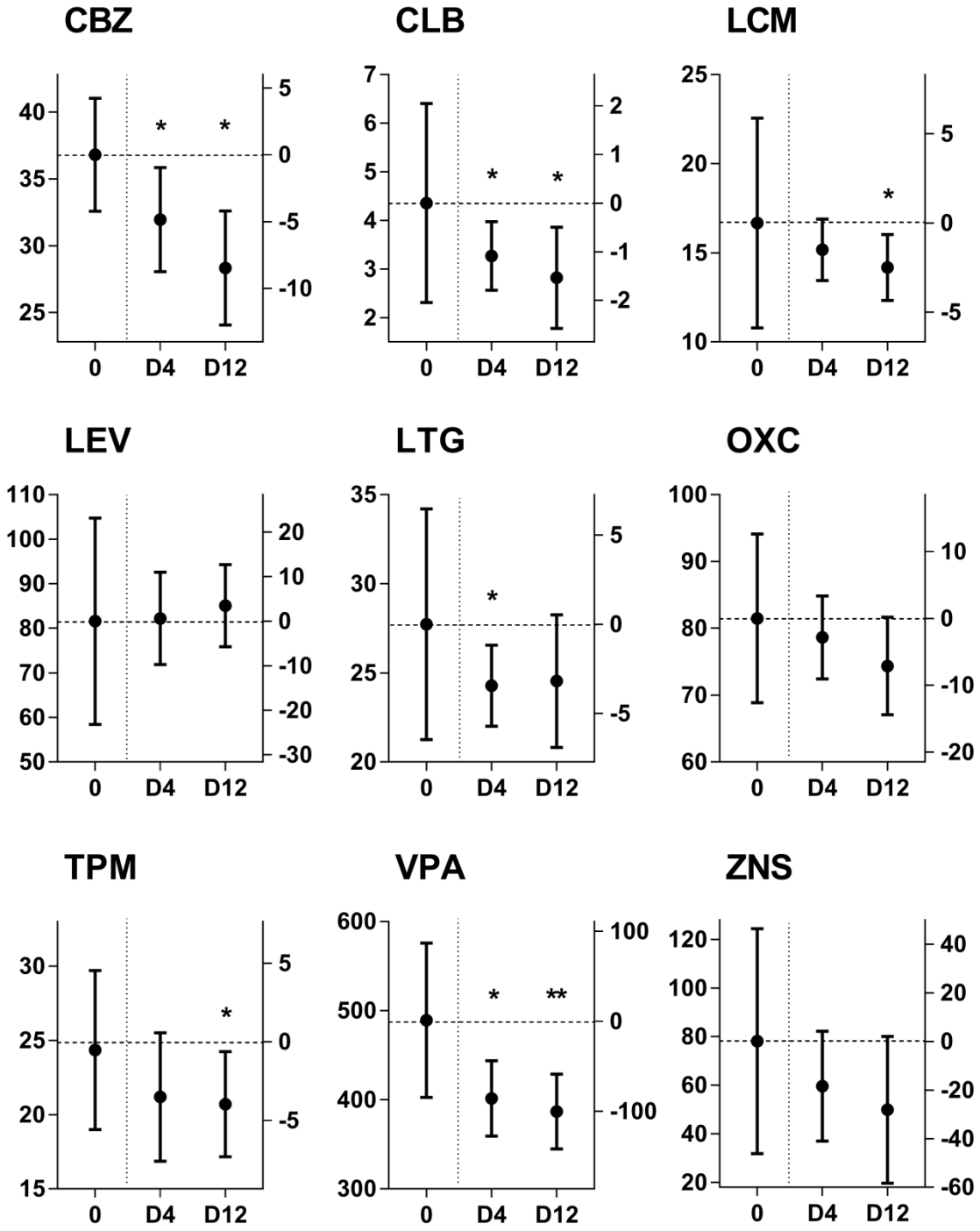

CBZ
CLB
LCM
LEV
LTG
OXC
TPM
VPA
ZNS
0
D4
D12
*
**

FIGURE S2: Mean (95% CI) of levels of ketosis and glucose at baseline and after 4 and 12 weeks of treatment with modified Atkins diet. A) Morning urine ketosis; B) Evening urine ketosis; C) Morning blood ketosis; D) Evening blood ketosis; E) Morning blood glucose; F) Evening blood glucose; G) Venous fasting glucose; H) HbA1c. Paired t-test was used to compare values at 4 and 12 weeks versus baseline, and at 12 weeks versus 4 weeks: * $0.001 \leq p < 0.05$; ** $p < 0.001$.

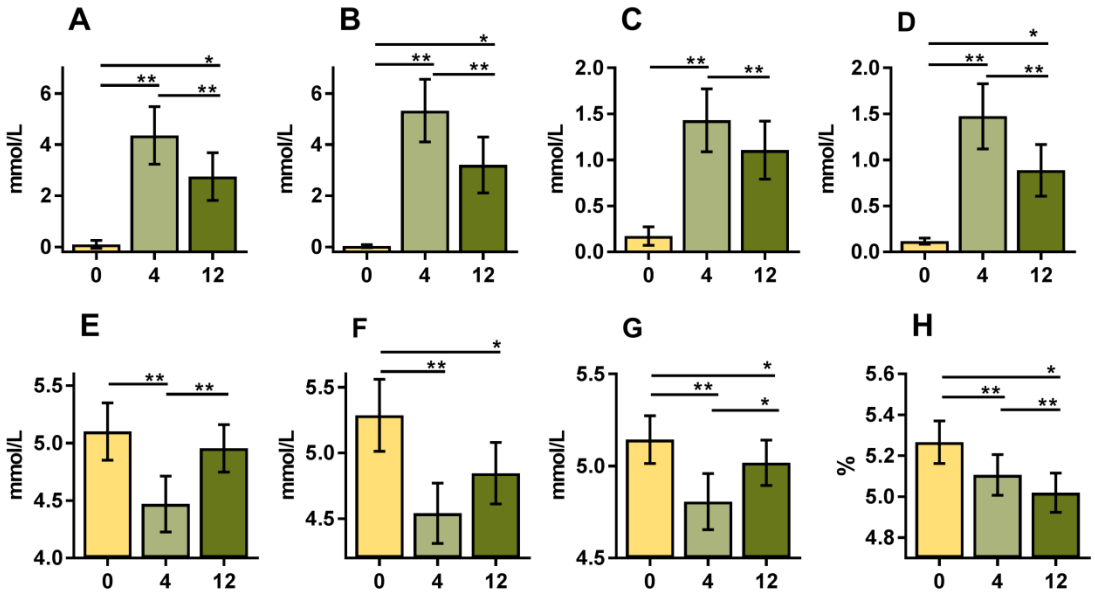


TABLE S1 Spearman's correlation between per cent change in serum concentration of all AEDs (excluding LEV) and ketosis, both measured in the morning and evening, in urine and in blood, after four and twelve weeks of treatment, self-assessed at home and during admission. Fasting glucose and HbA1c was assessed in venous blood

	4 weeks	**12 weeks**
Morning self-assessed average urine ketosis	r=-0.41; p=0.005; n=46	r=-0.43; p=0.003; n=46
Evening self-assessed average urine ketosis	r=-0.40; p=0.005; n=46	r=-0.48; p=0.001; n=46
Morning urine ketosis	r=-0.41; p=0.004; n=46	r=-0.28; p=0.06; n=45
Evening urine ketosis	r=-0.43; p=0.004; n=43	r=-0.36; p=0.02; n=44
Morning blood ketosis	r=-0.34; p=0.01; n=50	r=-0.23; p=0.11; n=48
Evening blood ketosis	r=-0.19; p=0.20; n=47	r=-0.27; p=0.07; n=47
Morning blood glucose	r=0.32; p=0.02; n=51	r=0.27; p=0.05; n=51
Evening blood glucose	r=0.15; p=0.30; n=48	r=0.32; p=0.03; n=45
Fasting blood glucose	r=0.20; p=0.14; n=56	r=0.22; p=0.10; n=54
HbA1c (change)	r=0.11; p=0.43; n=56	r=0.27; p=0.05; n=54

FIGURE S3A Scatter plot of per cent change in AED serum concentrations (excluding LEV) and ketosis, morning and evening, in urine and in blood, after four and twelve weeks of treatment, during admission. Blood ketose was assessed by finger-prick in ward during admission. A. Morning urine ketosis. B. Evening urine ketosis. C. Morning blood ketosis. D. Evening blood ketosis

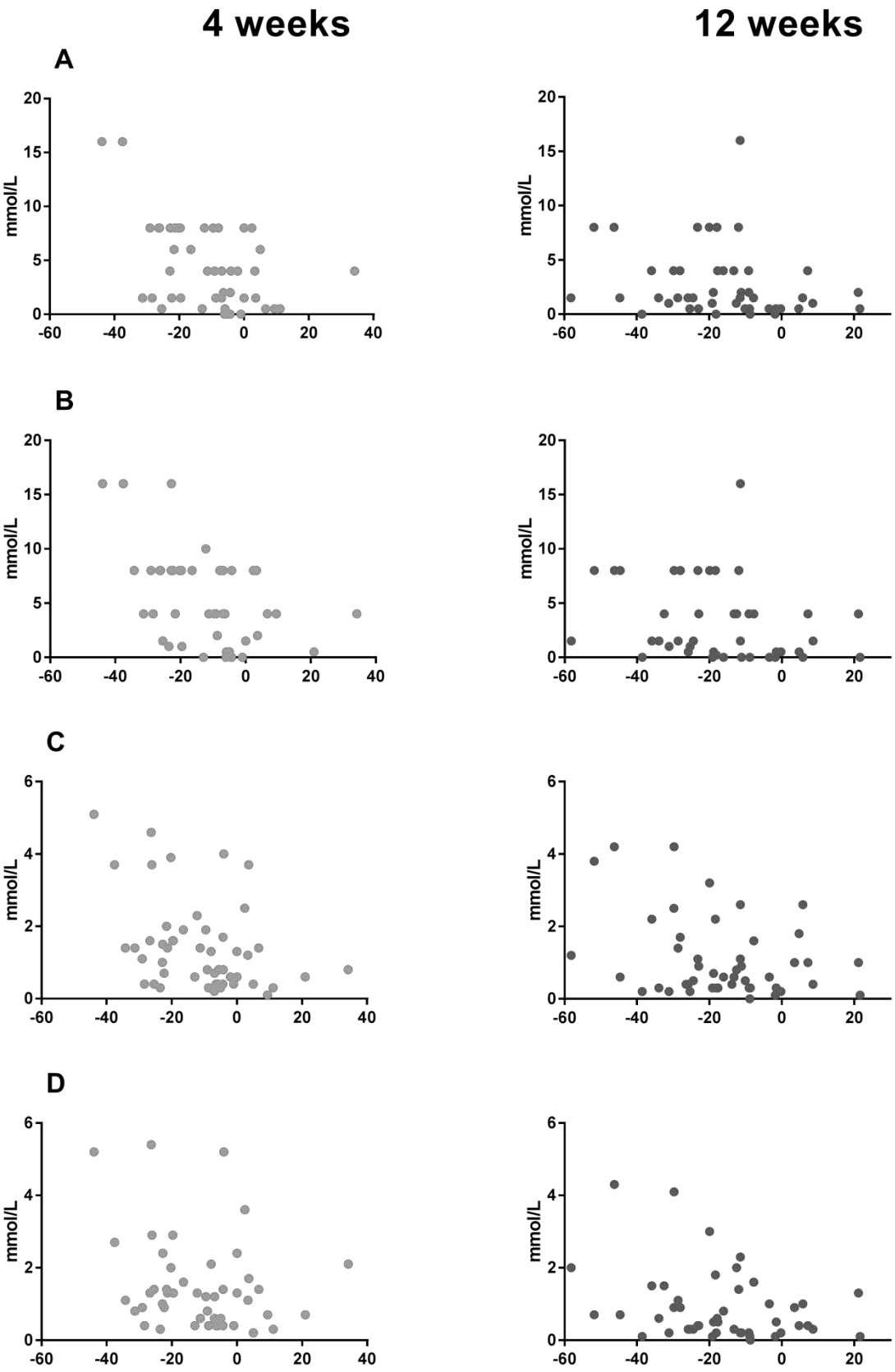

4 weeks
12 weeks
A
B
C
D
mmol/L
20
15
10
5
0
6
4
2
-60
-40
-20
0
20
40

FIGURE S3B Scatter plot of per cent change in AED serum concentrations (excluding LEV) and self-assessed urine ketosis, using urine dipsticks measured in the (A) morning and (B) evening daily during 12 weeks on diet, mean values calculated after four and twelve weeks of treatment

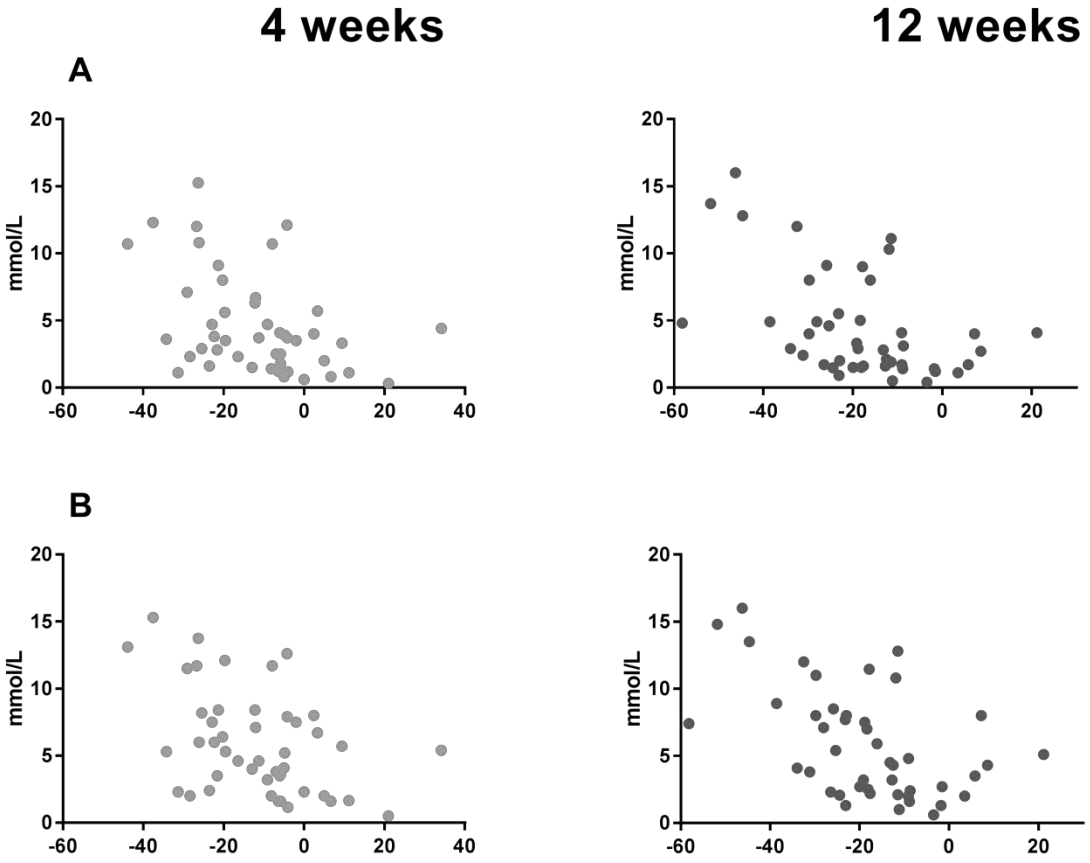
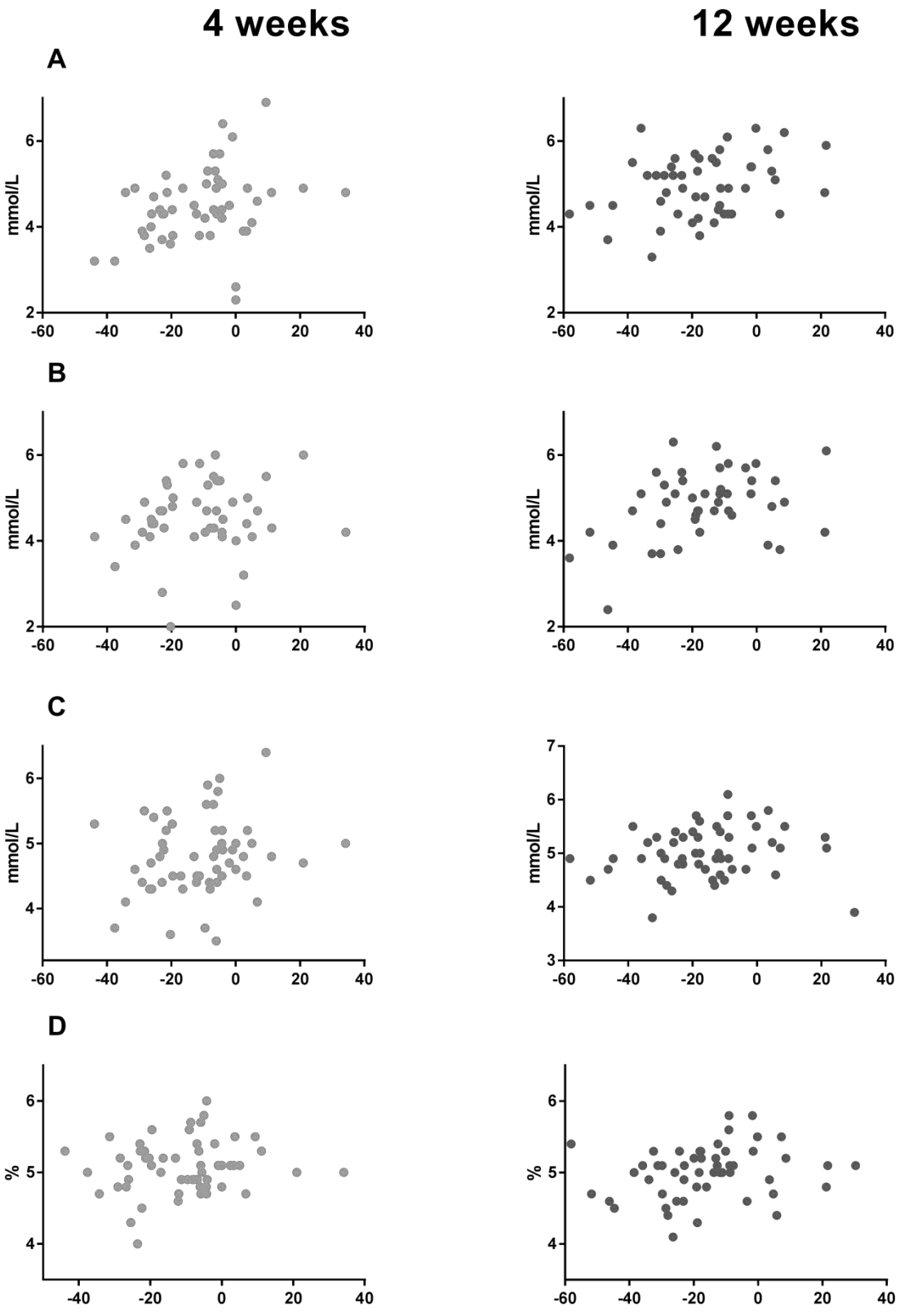


FIGURE S3C Scatter plot of per cent change in AED serum concentrations (excluding LEV) and blood glucose/HbA1c, both measured in the morning and evening, after four and twelve weeks of treatment, during admission. Morning/evening glucose was assessed in finger-prick and measured in ward during admission, while fasting glucose and HemoglobinA1c was assessed in venous blood and analyzed in laboratory. A. Morning glucose B. Evening glucose. C. Venous sample fasting glucose D. Hemoglobin A1c


4 weeks
12 weeks
A
B
C
D
mmol/L
%

APPENDIX

Forespørsel om deltakelse i forskningsprosjektet

Effekt av modifisert Atkins diett ved behandlingsrefraktær epilepsi hos voksne

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i en forskningsstudie for å studere effekten av modifisert Atkins diett blant voksne med epilepsi som ikke oppnår tilfredsstillende effekt av medisiner og annen behandling. Ved Avdeling for kompleks Epilepsi – SSE (AKE-SSE), Oslo universitetssykehus, som er ansvarlig for studien, har vi tilbud om diettbehandling for barn, men til nå har dette ikke vært tilbudt voksne. Modifisert Atkins diett har vist seg å ha en god anfallsreduserende effekt hos barn, og man har sett lignende effekt på voksne. Dietten innebærer et høyt inntak av fettrik mat, og begrenset inntak av karbohydratrike matvarer som brød og andre kornvarer, pasta, ris, melk og frukt. Du vil få grundig opplæring i dietten, og det finnes gode alternativer for brød og de fleste andre vanlige retter. Rent kjøtt, fisk, egg og en del oster kan du spise ubegrenset. Vi ønsker å inkludere personer som er motivert til å forsøke diettbehandling, og som har mulighet for selv å lage maten, eventuelt andre som kan tilberede maten for deg.

Alternativ til å delta i prosjektet er fortsettelse av nåværende behandling.

Hva innebærer studien?

For deltakere i studien vil det innebære en periode med anfallsregistrering og deretter oppstart av modifisert Atkins diett. Det er et mål å stå på dietten i 12 uker for å kunne vurdere om den har effekt. Dersom du ønsker å fortsette med dietten etter dette, vil du få videre oppfølging ved AKE-SSE.

Det må ikke gjøres endring i medisinering verken i perioden med anfallsregistrering eller de tre månedene på diett. Før oppstart må det gjennomføres en ultralydundersøkelse av nyrene ved lokalt sykehus for å utelukke nyresten.

Like før diettoppstart inviteres deltaker til tre dagers innleggelse ved AKE-SSE, Solbergtoppen eller post 2, uken før diettoppstart. Nære pårørende er også velkomne til å delta på undervisningen. Ved innleggelsen gjøres følgende:

- blodprøver,
- 3-timers standard EEG,
- gruppeundervisning i diett og matlagingskurs ved behov (1 – 4 deltakere),
- måle høyde og vekt,
- fylle ut skjema om livskvalitet, eksekutivfunksjoner og anfallsalvorlighetsgrad

Etter oppholdet reiser du hjem for å starte på dietten den påfølgende mandag. Du får med deg nødvendig utstyr som kjøkkenvekt, kosttilskudd, urinstix og matoppskrifter. Urinketose og anfall registreres daglig. Klinisk ernæringsfysiolog eller sykepleier tilbyr telefonisk oppfølging den første tiden etter oppstart, og senere etter behov.
Etter to og ti uker på diett ber vi deg om å skrive ned alt du spiser i tre dager. Eget skjema finnes til dette. Det er viktig at du noterer vekten på alt du spiser disse dagene. Kostregistreringene tas med til kontroll ved AKE-SSE etter henholdsvis 4 og 12 uker. Da tas det nye blodprøver, 3-timers standard EEG og skjema om livskvalitet, eksekutivfunksjoner og anfallsalvorlighetsgrad fylles ut.
Dersom du som deltaker, i samråd med lege og klinisk ernæringsfysiolog finner at du må bryte dietten før det har gått tre måneder, inviteres du til innleggelse ved AKE-SSE der man foretar blod- og urinprøver, fyller ut spørreskjema og gjennomfører 3-timers standard EEG.

To studiegrupper

Etter at du har samtykket til å delta i studien vil du som deltager fordeles tilfeldig til en av to grupper: diettgruppe og kontrollgruppe. Det har betydning for forløpet av din deltagelse i prosjektet. Diettgruppen fører anfallskalender i tolv uker (basisperioden), starter deretter på dietten (diettperioden) og følger denne i tolv uker. Kontrollgruppedeltakere skal også registrere anfall i basisperioden, men de fortsetter å spise vanlig kost og registrere anfall i tolv uker til (kontrollperioden), før de deretter starter på diett. Oppfølgingen med hensyn på diettbehandlingen er den samme for de to gruppene.

Mulige fordeler og ulemper

Mulige fordeler av diettbehandlingen er redusert anfallsfrekvens, redusert varighet og alvorlighetsgrad av anfall. Noen blir mer opplagte og får bedre konsentrasjonsevne av å stå på diett. Dersom det er ønskelig og medisinsk forsvarlig, kan man gå ned i vekt mens man står på dietten. Hos noen kan dietten gi anfallsfrihet, og nedtrapping av medisiner kan vurderes.
Noen opplever ubehag i form av kvalme, diaré, slapphet den første uken på diett. Det kan også forekomme en forbigående anfallsøkning. Det å stå på en streng diett er arbeidskrevende og medfører at man må planlegge de fleste måltider, også når man skal ut og spise i sosiale sammenhenger.

Bivirkninger av modifisert Atkins diett

Man antar at modifisert Atkins diett vil kunne gi færre bivirkninger enn ketogen diett fordi denne er mindre restriktiv. I de få studiene som er gjennomført på voksne er det ikke rapportert om alvorlige bivirkninger eller avvikende laboratorieprøver. Mange opplever vektnedgang, og for de fleste er dette en ønsket effekt. Forstoppelse er nevnt som en bivirkning ved ketogen diett hos barn. Vår erfaring er imidlertid at dette ikke er noe problem blant voksne som har et adekvat inntak av løselig fiber og væske.

Metabolsk acidose (blodet forsures) er en forbigående effekt av dietten som kan gi ubehag de første dagene etter diettstart. Blant barn på ketogen diett har man sett økt forekomst av nyrestein og en forbigående forhøyelse av blodets fettstoffer (kolesterol og triglyserider). Du vil få kaliumsitrat for å forebygge nyresten, og fettstoffene følges opp ved hjelp av blodprøver.

Et fullverdig kosthold skal gi adekvat inntak av alle essensielle næringsstoffer. På modifisert Atkins diett vil kosten bli ensidig, spesielt på grunn av lavt inntak av kornprodukter, frukt og grønnsaker. Alle deltakere må ta tilskudd av multivitaminer, og i studien har vi vurdert tilgjengelige produkter og valgt det som er best egnet. Tran eller trankapsler er mye brukt som tilskudd av langkjedede fiskefettsyrer og vitamin D i Norge, og anbefales til deltakerne i studien.

Av langtidseffekter er det data som viser redusert bentetthet av ketogen diett. For å forebygge dette vil alle deltakere i studien få tilskudd av kalsiumkarbonat og vitamin D etter behov.

Hva skjer med prøvene og informasjonen om deg?

Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Dataene skal anonymiseres etter at prosjektet er avsluttet og resultatene er publisert, senest i 2022. Man skal ikke kunne identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte:

Prosjektleder

Karl Otto Nakken, Overlege dr. med
Avdeling for kompleks epilepsi, SSE
Klinikk for kirurgi og nevrofag
Telefon: 67501000

Prosjektmedarbeider
Magnhild Kverneland, Klinisk ernæringsfysiolog
Avdeling for kompleks epilepsi, SSE
Klinikk for kirurgi og nevrofag
Telefon: 67501000

Prosjektmedarbeider
Caroline Bruun Helland, Assistentlege
Avdeling for kompleks epilepsi, SSE
Klinikk for kirurgi og nevrofag
Telefon: 67501000

Ytterligere informasjon om studien finnes i kapittel *A* – *utdypende forklaring av hva studien innebærer.*
Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B – *Personvern, biobank, økonomi og forsikring.*

Samtykkeerklæring følger etter kapittel B.

Kapittel A- utdypende forklaring av hva studien innebærer

Bakgrunnsinformasjon

Historisk sett har det lenge vært kjent at faste og sult, med derav følgende ketose, kan ha en gunstig effekt på epilepsi. Imidlertid er det først de siste par tiårene at man har fått vitenskapelig dokumentasjon på at ulike dietter som gir ketose, spesielt ketogen diett hos barn, har en anfallsreduserende effekt. Det er også mye som tyder på at en lettere gjennomførbar variant av ketogen diett, kalt modifisert Atkins diett, kan ha god effekt på voksne.

Detaljert om studien

Informasjonssamtale gjennomføres 1 til tre måneder før du eventuelt blir inkludert i prosjektet. Samtalen og skriftlig informasjon skal gi deg nok grunnlag til å vurdere om du ønsker å delta. Dersom du beslutter å delta, signerer du på dette samtykkeskjemaet og returnerer det til AKE-SSE ved Magnhild Kverneland. Etter inklusjon trekkes du til diett- eller kontrollgruppe. For den som tildeles å være med i diettgruppen vil studien bestå av to 12-ukersperioder: basisperioden og diettperioden. Kontrollgruppedeltakerne må gjennomføre tre 12-ukersperioder: basisperioden, kontrollperioden og diettperioden. Nedenfor er hver av periodene beskrevet. I alle periodene må annen behandling holdes konstant.

Basisperioden

Basisperioden består av 12 uker nøyaktig anfallsregistrering. Du fortsetter å spise det samme som før i denne perioden.

Kontrollperioden

Du fortsetter å spise det samme som før i kontrollperioden.

Kort innleggelse med blodprøver, spørreskjema, 3-timers standard EEG	Uke 1
Telefonoppfølging fra AKE-SSE	Uke 3 – 4
3-dagers kostregistrering	Uke 4
Telefonoppfølging fra AKE-SSE	Uke 9-10

Uke 12 i kontrollperioden er uken før diettoppstart i diettperioden.

Diettperioden

Nyre ultralyd ved lokalt sykehus	1 – 3 måneder før diettoppstart
3-dagers innleggelse med opplæring, blodprøver, spørreskjema, 3-timers standard EEG	En uke før diettoppstart
Oppstart på diett hjemme med daglig anfallskalender og	Uke 0

urinketosemåling	
3-dagers kostregistrering	Uke 2-3
Kort innleggelse med blodprøver	Uke 4
3-dagers kostregistrering	Uke 10-11
Kort innleggelse med blodprøver, spørreskjema, 3-timers standard EEG	Uke 12

Deltakers ansvar

Det forventes at du som deltaker gjør et helhjertet forsøk på å leve på diett i 12 uker. Dersom du ønsker å avslutte dietten før avtalt tid, forventes du å ta kontakt med en av prosjektets kontaktpersoner før dietten avsluttes.

Kriterier for deltakelse i studien:

Inklusjonskriterier:

- Sikker fokal eller generalisert epilepsi
- Anfallsfrekvens > 3 anfall/måned (observerbare fokale eller generaliserte)
- BMI > 18,5
- Forsøkt minst 3 antiepileptika uten å ha oppnådd anfallskontroll.
- Alder >16 år
- Motivert for gjennomføring av studien etter grundig informasjon
- I stand til å gjennomføre diett og å kunne føre nøyaktig anfallskalender (på egenhånd eller vha. pårørende)
- Pasienten eller pårørende er i stand til å lage diettmat, eller har tilstrekkelig hjelp til matlaging.

Eksklusjonskriterier:

- Kjent hyperkolesterolemi, hjerte-kar sykdom eller nyresykdom
- Tidligere brukt Atkins diett >1 uke eller ketogen diett siste år
- Status epilepticus de siste 6mndr
- Epilepsikirurgi, inkludert VNS (vagus nervestimulator) siste år
- 4 uker sammenhengende anfallsfrihet de siste 2 måneder
- PNES (psykiske ikke-epileptiske anfall) i tillegg til epilepsi
- Annen sykdom/tilstand der diettbehandling er kontraindisert
- Bruk av legemiddel/naturmedisiner som kan interagere med diett og/eller antiepileptika
- Graviditet/graviditet planlegges i løpet av diettperioden

Kriterier for å avbryte studien:

- Klar forverring av anfallssituasjon
- Ikke tolererbare bivirkninger
- Endring av den antiepileptiske medikasjon under registreringsperioden
- Annen sykdom som oppstår under diettbehandlingen
- Pasienten ønsker selv å avbryte dietten
- Nyoppstått graviditet

Kapittel B - Personvern, biobank, økonomi og forsikring

Personvern

Opplysninger som registreres om deg er all informasjon som vi får fra deg i løpet av studieperioden: anfallskalender, livskvalitetsskjema, skjema for eksekutivfunksjoner, anfallsalvorlighetsgradsskjema, kostregistrering og blodprøvesvar. Det forskes mye på ketogen diett og modifisert Atkins diett i hele verden, så i tillegg til de blodprøvene som analyseres fortløpende ønsker vi å fryse ned litt blod fra deg som vi kan bruke til spesielle analyser etter at prosjektet er avsluttet. Disse blodprøvene skal benyttes til å finne ut mer om hvordan modifisert Atkins diett virker på kroppen. Datamaterialet som samles inn skal bare benyttes av autorisert personell som har avlagt taushetserklæring og som også har tilgang til journalen ved AKE-SSE. Oslo Universitetssykehus ved administrerende direktør er databehandlingsansvarlig.

Biobank

Blodprøvene som blir tatt og informasjonen utledet av dette materialet vil bli lagret i en forskningsbiobank ved Avdeling for kompleks epilepsi. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Svein I. Johannessen ved klinisk kjemisk laboratorium, AKE-SSE er ansvarshavende for forskningsbiobanken. Biobanken planlegges å vare til 2022. Etter dette vil materiale og opplysninger bli destruert og slettet etter interne retningslinjer.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Informasjon om utfallet av studien

Som deltaker i studien har du rett til å få informasjon om resultatet av studien.

Samtykke til deltakelse i diettstudien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Stedfortredende samtykke når berettiget, enten i tillegg til personen selv eller istedenfor

---

(Signert av nærstående, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Modifisert Atkins diett for voksne

Anfallsregistrering under diettperiode

Deltager nr _____ År 20 __

Dokumentasjon av anfall må gjøres nøyaktig og systematisk i prosjektet.
Det kreves tallmateriale for å måle effekten av dietten. Dvs. antall og varighet.

Anfallsoversikt

Lag en oversikt over de anfallene som pasienten har. Bruk vedlagte skjema.

Beskriv:

- symptomer
- varighet
- hyppighet
- serieanfall?

Anfallsregistrering

Start med å registrere anfall 12 uker før oppstartsinnleggelse. Registrer alle anfall daglig på vedlagte anfallskalender.

Ved svært **hyppige anfall:**
Velg ut ½ time hver dag hvor du pleier å ha mye
anfall og registrer alle anfall. Registrer på samme tid hver dag i hele perioden.

Varighet:
Skriv en samlet kommentar hver uke dersom anfall varer kortere eller lengre enn angitt i anfallsoversikten.

Anfallsoversikt

Deltager nr---------

Anfallstype	
Symptomer	
Varighet	
Hyppighet	
Anfallstype	
Symptomer	
Varighet	
Hyppighet	
Anfallstype	
Symptomer	
Varighet	
Hyppighet	

Anfallsoversikt

Deltager nr---------

Anfallstype	
Symptomer	
Varighet	
Hyppighet	
Anfallstype	
Symptomer	
Varighet	
Hyppighet	
Anfallstype	
Symptomer	
Varighet	
Hyppighet	

Anfallskalender

Deltager nr---------

Uke 1	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender **Deltager nr---------**

Uke 2	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender **Deltager nr---------**

Uke 3	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender **Deltager nr---------**

Uke 4	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender

Deltager nr---------

Uke 5	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender

Deltager nr---------

Uke 6	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender **Deltager nr---------**

Uke 7	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender **Deltager nr---------**

Uke 8	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender **Deltager nr---------**

Uke 9	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender

Deltager nr---------

Uke 10	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender

Deltager nr---------

Uke 11	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender

Deltager nr---------

Uke 12	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Anfallskalender **Deltager nr---------**

Uke 12	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag	
Dag, mnd								
Urinketose morgen								
Urinketose kveld								
Anfall, type/antall								**Sum**
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Anfall, type/antall								
Endret varighet								
OPPLYSNINGER SOM FYLLES UT NÅR AKTUELT:								
Gitt Stesolid / Epistatus, antall doser								
Infeksjon								
Vekt (ukentlig) kg								

Returneres ferdig utfylt til
Magnhild Kverneland
Avdeling for kompleks epilepsi – SSE
Oslo Universitetssykehus
Telefon: 67501000

DeltakerID:_____

Dato: _____

Liverpool Seizure Severity Scale

Vi ber deg her om å beskrive anfallene dine ved å se gjennom punktene 1 til 12 under og merke av den beskrivelsen som passer best for deg. Vi er opptatt av de *sterkeste* anfallene. Forskjellige mennesker bruker forskjellige ord når de snakker om anfall, og andre ord for de *sterkeste* anfallene er de *kraftigste*, *hardeste*, *største*, osv.

Tenk på de **sterkeste** anfallene du har hatt **de siste 3 månedene**, og sett ring rundt det alternativet som passer best. **Sett bare én ring under hvert punkt**.

1. Mine sterkeste anfall har stort sett vært
   - 0 Veldig sterke
   - 1 Sterke
   - 2 Forholdsvis lette
   - 3 Svært lette

2. Når jeg mister bevisstheten / blir borte varer det som regel
   - 1 Mindre enn ett minutt
   - 2 Mellom 1 og 2 minutter
   - 3 Mellom 3 og 5 minutter
   - 4 Mer enn 5 minutter
   - 0 Nei, jeg mister aldri bevisstheten / blir aldri borte

3. Når jeg har mine sterkeste anfall smatter jeg, eller jeg fikler med ting, eller jeg oppfører meg på en uvanlig måte
   - 0 Alltid
   - 1 Vanligvis
   - 2 Av og til
   - 3 Aldri

4. Etter mine sterkeste anfall føler jeg meg
   - 0 Svært forvirret
   - 1 Nokså forvirret
   - 2 Litt forvirret
   - 3 Nei, ikke forvirret i det hele tatt

5. Etter mine sterkeste anfall varer forvirringen
   - 1 Mindre enn 1 minutt
   - 2 Mellom 1 og 5 minutter
   - 3 Mellom 5 minutter og 1 time
   - 4 Mellom 1 og 2 timer
   - 5 Mer enn 2 timer
   - 0 Nei, jeg er aldri forvirret etter anfall

6. Når jeg har mine sterkeste anfall
   - 0 Faller jeg alltid overende
   - 1 Faller jeg ofte overende
   - 2 Faller jeg av og til overende
   - 3 Nei, jeg faller aldri overende under anfall

7. Etter mine sterkeste anfall
   - 0 Får jeg alltid hodepine
   - 1 Får jeg vanligvis hodepine
   - 2 Får jeg av og til hodepine
   - 3 Nei, jeg får aldri hodepine etter anfallene

8. Etter mine sterkeste anfall
   0 Blir jeg alltid søvnig eller trett
   1 Blir jeg oftest søvnig eller trett
   2 Blir jeg av og til søvnig eller trett
   3 Nei, jeg blir aldri søvnig eller trett etter anfallene

9. Etter mine sterkeste anfall oppdager jeg at jeg har tisset på meg
   0 Alltid
   1 Ofte
   2 Av og til
   3 Nei, jeg tisser aldri på meg under anfallene

10. Etter mine sterkeste anfall oppdager jeg at jeg har bitt meg i tungen eller i kinnet
   0 Alltid
   1 Ofte
   2 Av og til
   3 Nei, jeg biter meg aldri i tungen eller i kinnet under de sterkeste anfallene

11. Etter mine sterkeste anfall oppdager jeg at jeg har skadet meg på andre måter enn å bite meg i kinnet eller i tungen
   0 Alltid
   1 Ofte
   2 Av og til
   3 Nei, jeg skader meg aldri på andre måter enn å bite meg i tungen eller kinnet

12. Etter mine sterkeste anfall greier jeg vanligvis å fortsette med det jeg holdt på med før anfallet
   0 Mindre enn 1 minutt etter anfallet
   1 Når det er gått mellom 1 og 5 minutter etter anfallet
   2 Når det er gått mellom 6 minutter og 1 time etter anfallet
   3 Når det er gått mellom 1 time og 2 timer etter anfallet
   4 Mer enn 2 timer etter anfallet

Returneres ferdig utfylt til
Magnhild Kverneland
Avdeling for kompleks epilepsi – SSE
Oslo Universitetssykehus
Telefon: 67501000

Returneres ferdig utfylt til
Magnhild Kverneland
Avdeling for kompleks epilepsi – SSE
Oslo Universitetssykehus
Telefon: 67501000

Epilepsiprosjektet
Nevrologisk avd.

DeltakerID:_____

Dato: _____

1-4

LIVSKVALITET VED EPILEPSI
QOLIE-89 (*Versjon 1.0*)

Pasient spørreskjema

Dagens dato |_|_|_|_|_|_|
Dag Mnd. År

5-10

Kjønn: ☐ **Mann (1)** ☐ **Kvinne (2)**

11

INSTRUKSJONER

Denne undersøkelsen spør om din helse og daglige aktiviteter. **Svar på alle spørsmålene** ved å sette en ring rundt det tallet som passer best (1, 2, 3...).

Hvis du er usikker på hvordan du skal svare på et spørsmål, svar så godt du kan og skriv en kommentar eller forklaring i margen.

Du må gjerne be noen om å hjelpe deg om du trenger hjelp til å lese eller sette ringer rundt tallene.

1. Stort sett, vil du si at helsa di er: (Sett ring rundt ett tall)

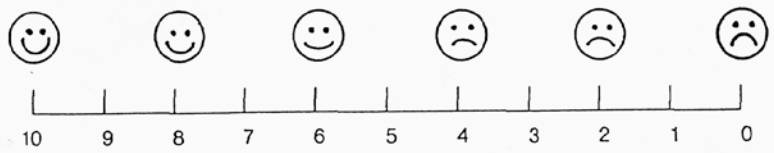
12

Utmerket	1
Meget god	2
God	3
Ganske god	4
Dårlig	5

2. Totalt sett, hvordan vurderer du din livskvalitet?

(Sett ring rundt ett tall på skalaen nedenfor)

13-14



Best mulige livskvalitet

Verst mulige livskvalitet (like dårlig som eller verre enn å være død)

3. **Sammenlignet med for 1 år siden**, hvordan vil du si at helsa di stort sett er **nå**?

(Sett ring rundt ett tall) *15*

Mye bedre nå enn for 1 år siden	1
Litt bedre nå enn for 1 år siden	2
Omtrent den samme som for 1 år siden	3
Litt dårligere nå enn for 1 år siden	4
Mye dårligere nå enn for 1 år siden	5

4-13: De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er **helsa di** slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, **hvor mye**?

(Sett ring rundt 1, 2 eller 3 på hver linje)

		Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt	
4.	*Anstrengende aktiviteteter*, som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	1	2	3	*16*
5.	*Moderate aktiviteter* som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid	1	2	3	*17*
6.	Løfte eller bære en handlekurv	1	2	3	*18*
7.	Gå opp trappen *flere* etasjer	1	2	3	*19*
8.	Gå opp trappen *en* etasje	1	2	3	*20*
9.	Bøye deg eller sitte på huk	1	2	3	*21*
10.	Gå *mer enn to kilometer*	1	2	3	*22*
11.	Gå *noen hundre meter*	1	2	3	*23*
12.	Gå *hundre meter*	1	2	3	*24*
13.	Vaske deg eller kle på deg	1	2	3	*25*

De neste spørsmålene er om dine vanlige daglige aktiviteter, som å arbeide i en jobb, holde huset i orden, ta vare på barn, gå på skolen, drive med frivillig arbeid, eller ta del i andre aktiviteter.

14-18: I løpet av **de siste 4 ukene**, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål **på grunn av din fysiske helse**? (Vennligst svar **JA eller NEI** for hvert spørsmål ved å sette ring rundt 1 eller 2 på hver linje.)

		JA	NEI	
14.	Har du redusert *tiden* du har brukt på arbeidet ditt eller andre aktiviteter	1	2	*26*
15.	Har du *utrettet mindre* enn du hadde ønsket	1	2	*27*
16.	Har du vært hindret i visse *typer* arbeid eller andre aktiviteter	1	2	*28*
17.	Har du hatt *vanskeligheter* med å utføre arbeidet ditt eller andre aktiviteter (f. eks. fordi det krevde ekstra anstrengelser)	1	2	*29*
18.	Har ikke arbeidet eller utført andre aktiviteter like *nøye* som vanlig	1	2	*30*

19-23: I løpet av **de siste 4 ukene**, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål **på grunn av følelsesmessige problemer** (f.eks. fordi du har følt deg deprimert eller engstelig)? (Vennligst svar **JA eller NEI** for hvert spørsmål ved å sette ring rundt 1 eller 2 på hver linje)

		JA	NEI	
19.	Har du redusert *tiden* du har brukt på arbeidet ditt eller andre aktiviteter	1	2	*31*
20.	Har du *utrettet mindre* enn du hadde ønsket	1	2	*32*
21.	Har du vært hindret i visse *typer* arbeid eller andre aktiviteter	1	2	*33*
22.	Har du hatt *vanskeligheter* med å utføre arbeidet ditt eller andre aktiviteter (f. eks. fordi det krevde ekstra anstrengelser)	1	2	*34*
23.	Har ikke arbeidet eller utført andre aktiviteter like *nøye* som vanlig	1	2	*35*

24. Hvor sterke **kroppslige smerter** har du hatt i løpet av **de siste 4 ukene?**

	(Sett ring rundt ett tall)	36
Ingen	1	
Meget svake	2	
Svake	3	
Moderate	4	
Sterke	5	
Meget sterke	6	

25. I løpet av **de siste 4 ukene**, hvor mye har **smerter** påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

	(Sett ring rundt ett tall)	37
Ikke i det hele tatt	1	
Litt	2	
Endel	3	
Mye	4	
Svært mye	5	

26. I løpet av **de siste 4 ukene**, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

	(Sett ring rundt ett tall)	38
Ikke i det hele tatt	1	
Litt	2	
Endel	3	
Mye	4	
Svært mye	5	

27-35: De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det **de siste 4 ukene**. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det.

Hvor ofte i løpet av **de siste 4 ukene** har du...

(Sett en ring rundt ett tall på hver linje)

		Hele tiden	Nesten hele tiden	Mye av tiden	Endel av tiden	Litt av tiden	Ikke i det hele tatt	
27.	Følt deg full av tiltakslyst?	1	2	3	4	5	6	*39*
28.	Følt deg veldig nervøs?	1	2	3	4	5	6	*40*
29.	Vært så langt nede at ingenting har kunnet muntre deg opp?	1	2	3	4	5	6	*41*
30.	Følt deg rolig og harmonisk?	1	2	3	4	5	6	*42*
31.	Hatt mye overskudd?	1	2	3	4	5	6	*43*
32.	Følt deg nedfor og trist?	1	2	3	4	5	6	*44*
33.	Følt deg sliten?	1	2	3	4	5	6	*45*
34.	Følt deg glad?	1	2	3	4	5	6	*46*
35.	Følt deg trett?	1	2	3	4	5	6	*47*

36-43: I løpet av **de siste 4 ukene**, hvor mye av tiden...

(Sett ring rundt ett tall på hver linje)

		Hele tiden	Nesten hele tiden	Mye av tiden	Endel av tiden	Litt av tiden	Ikke i det hele tatt	
36.	Har din epilepsi begrenset din sosiale omgang (som det å besøke venner eller nære slektninger)?	1	2	3	4	5	6	*48*
37.	Har du hatt vanskelig for å konsentrere deg eller for å tenke?	1	2	3	4	5	6	*49*
38.	Har du hatt vansker med å holde oppmerksomheten på en aktivitet i lengre tid?	1	2	3	4	5	6	*50*
39.	Var du motløs på grunn av problemer forbundet med din helse?	1	2	3	4	5	6	*51*
40.	Har du vært bekymret for å få et nytt anfall?	1	2	3	4	5	6	*52*
41.	Har du hatt vansker med å resonnere og løse problemer (for eksempel lage planer, ta beslutninger, lære nye ting)?	1	2	3	4	5	6	*53*
42.	Har du vært motløs på grunn av problemer knyttet til din epilepsi?	1	2	3	4	5	6	*54*
43.	Har din fysiske helse eller følelsesmessige problemer påvirket dine sosiale aktiviteter (som det å besøke venner, slektninger, etc)?	1	2	3	4	5	6	*55*

44-48: Hvor **RIKTIG** eller **GAL** er hver av de følgende påstander for deg?

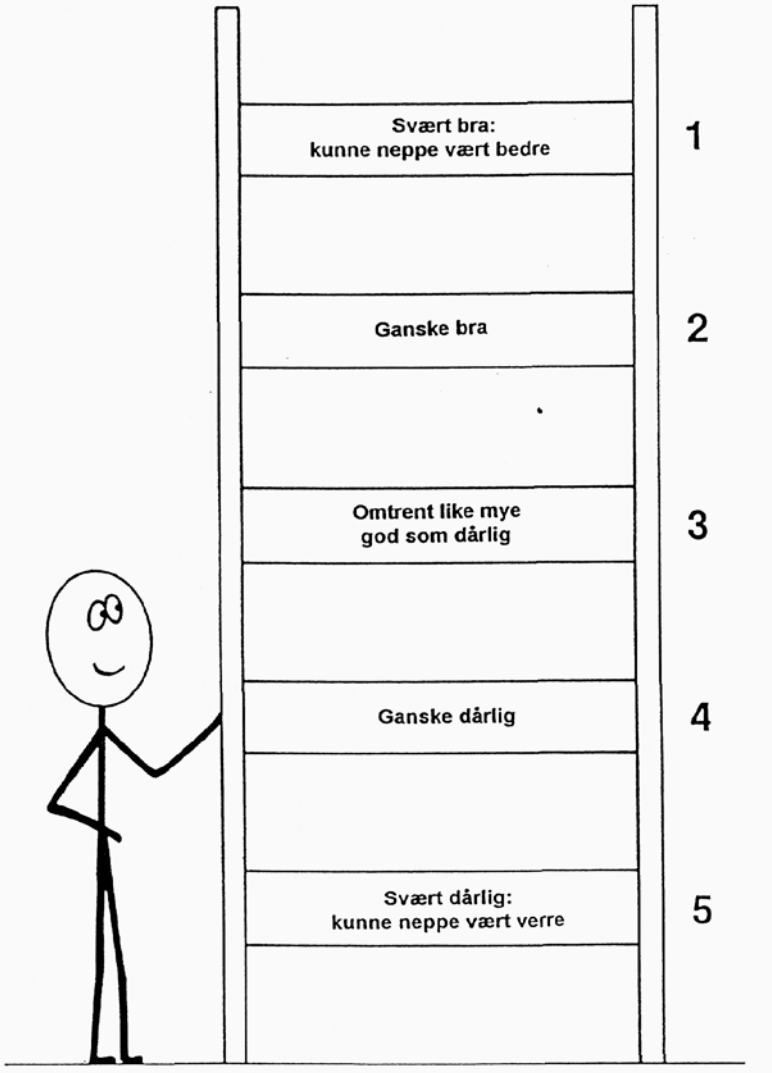
(Sett ring rundt ett tall på hver linje)

		Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal	
44.	Det virker som om jeg blir litt lettere syk enn andre	1	2	3	4	5	*56*
45.	Jeg er like frisk som de fleste jeg kjenner	1	2	3	4	5	*57*
46.	Jeg forventer at helsa mi vil bli dårligere	1	2	3	4	5	*58*
47.	Helsa mi er utmerket	1	2	3	4	5	*59*
48.	Når det er en sykdom som går, pleier jeg å få den	1	2	3	4	5	*60*

49. Hvordan har **LIVSKVALITETEN DIN** vært **de siste 4 ukene** (det vil si, hvordan har ting gått for deg)?

61

(Sett ring rundt ett tall)



Det neste spørsmålet er om **HUKOMMELSE**. (Sett ring rundt ett tall)

		Ja, en hel del	Ja, en del	Bare litt	Nei, ikke i det hele tatt	
50.	I løpet av de siste 4 ukene, har du hatt noen problemer med hukommelsen din?	1	2	3	4	*62*

51-54: Sett ring rundt ett tall for **hvor ofte** i løpet av **de siste 4 ukene** du har hatt problemer med *å huske* eller **hvor ofte** disse problemene med hukommelsen har hindret deg i ditt normale arbeid eller liv.

		Hele tiden	Det meste av tiden	En stor del av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt	
51.	Navn på personer	1	2	3	4	5	6	*63*
52.	Hvor du har lagt ting	1	2	3	4	5	6	*64*
53.	Ting folk forteller deg	1	2	3	4	5	6	*65*
54.	Ting du har lest timer eller dager tidligere	1	2	3	4	5	6	*66*

55-59: De neste spørsmålene er om **SPRÅKPROBLEMER** du kanskje har. Sett ring rundt ett tall for **hvor ofte** du har problemer med å snakke eller **hvor ofte** disse problemene hindrer deg i ditt normale arbeid eller liv.

		Hele tiden	Det meste av tiden	En stor del av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt	
55.	Å finne det riktige ordet	1	2	3	4	5	6	*67*
56.	Å forstå hva andre sier i en samtale	1	2	3	4	5	6	*68*
57.	Å forstå instruksjoner	1	2	3	4	5	6	*69*
58.	Å forstå det du leser	1	2	3	4	5	6	*70*
59.	Å skrive	1	2	3	4	5	6	*71*

60-64: De neste spørsmålene handler om **KONSENTRASJONSPROBLEMER** du kanskje har. Sett ring rundt ett tall for **hvor ofte** i **de siste 4 ukene** du har hatt problemer med å konsentrere deg eller **hvor ofte** disse problemene har hindret deg i ditt normale arbeid eller liv.

		Hele tiden	Det meste av tiden	En stor del av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt	
60.	Konsentrere deg om samtaler	1	2	3	4	5	6	72
61.	Konsentrere deg om en oppgave eller jobb	1	2	3	4	5	6	73
62.	Konsentrere deg om å lese	1	2	3	4	5	6	74
63.	Konsentrere deg om å gjøre en ting om gangen	1	2	3	4	5	6	75
64.	Hvor ofte føler du at du reagerer langsomt på ting som sies eller gjøres?	1	2	3	4	5	6	76

65-68: De neste spørsmålene handler om problemer du kan ha med enkelte **AKTIVITETER**. Sett ring rundt ett tall for **hvor mye** i løpet av **de siste 4 ukene** din epilepsi eller antiepileptiske medikasjon har forårsaket problemer med...

		Svært mye	Mye	Endel	Bare litt	Ikke i det hele tatt	
65.	Å arbeide	1	2	3	4	5	77
66.	Vennskap og forhold (romantiske)	1	2	3	4	5	78
67.	Fritid (som hobbyer, å gå ut på noe)	1	2	3	4	5	79
68.	Bilkjøring	1	2	3	4	5	80

69-73: De neste spørsmålene handler om hva du **FØLER** overfor dine **anfall**.

(Sett ring rundt ett tall på hver linje)

		Svært redd	Ganske redd	Litt redd	Ikke redd i i det hele tatt	
69.	Hvor redd er du for å få et anfall i løpet av den neste måneden?	1	2	3	4	*81*

		Ofte bekymret	Av og til bekymret	Ikke bekymret i det hele tatt	
70.	Er du bekymret for å skade deg selv under et anfall?	1	2	3	*82*

		Svært bekymret	Ganske bekymret	Litt bekymret	Ikke bekymret i det hele tatt	
71.	Hvor bekymret er du for forlegenhet (havne i en pinlig situasjon) eller andre sosiale problemer som et resultat av å få et anfall i løpet av den neste måneden?	1	2	3	4	*83*
72.	Hvor bekymret er du for at medisinene du tar vil være skadelige for deg, om du bruker dem over lang tid?	1	2	3	4	*84*

		Svært t dårlig	Ikke så bra	Brukbart	Bra	Svært bra	
73.	Hvor godt håndterer du kompliserte aktiviteter som krever organisering og planlegging?	1	2	3	4	5	*85*

74-80: For hvert av disse **PROBLEMENE**, sett ring rundt et tall for **hvor mye de plager deg** på en skala fra 1 til 5, hvor 1= Ikke plagsom i det hele tatt, og 5= Ekstremt plagsomt.

		Ikke plagsomt i det hele tatt				Ekstremt plagsomt	
74.	Anfall	1	2	3	4	5	*86*
75.	Problemer med hukommelsen	1	2	3	4	5	*87*
76.	Begrensninger i mulighet for bilkjøring	1	2	3	4	5	*88*
77.	Begrensinger i arbeid	1	2	3	4	5	*89*
78.	Sosiale begrensninger	1	2	3	4	5	*90*
79.	Fysiske effekter av antiepileptisk medikasjon	1	2	3	4	5	*91*
80.	Mentale effekter av antiepileptisk medikasjon	1	2	3	4	5	*92*

81-83: Sett ring rundt ett tall for å svare på **hvor fornøyd du er med ditt familieliv og sosiale liv**:

		Lite	Sånn passe	Godt	Meget godt	Utmerket	
81.	Grad av fellesskap du har med din familie og/eller venner	1	2	3	4	5	*93*
82.	Støtte og forståelse din familie og/eller venner gir hverandre	1	2	3	4	5	*94*
83.	Hvor mye du får snakket ut med din familie og/eller venner	1	2	3	4	5	*95*

84-88: Når det gjelder **din tilfredshet med ditt familieliv og sosiale liv**, sett ring rundt ett tall for å svare på følgende:

		Svært fornøyd	Ganske fornøyd	Hverken fornøyd eller misfornøyd	Noe misfornøyd	Svært misfornøyd	
84.	Totalt sett, hvor fornøyd har du vært med dine seksuelle forhold **de siste 4 ukene**?	1	2	3	4	5	*96*

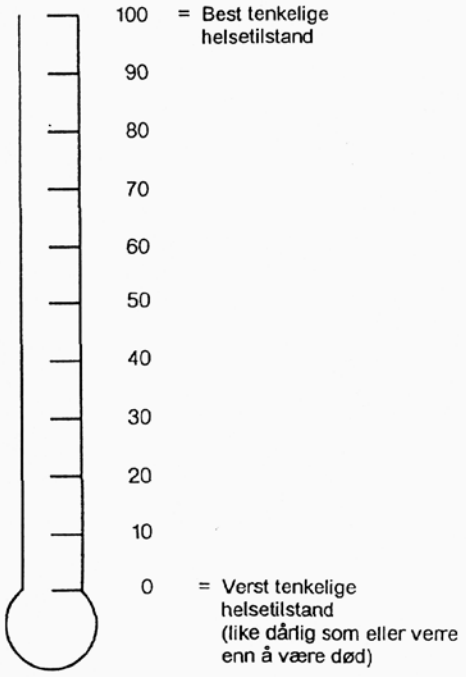
		Mye mer begrenset	Noe mer begrenset	Omtrent det samme	Noe mindre begrenset	Mye mindre begrenset	
85.	Hvor begrenset er dine sosiale aktiviteter sammenlignet med andre på din alder på grunn av din epilepsi eller problemer knyttet til din epilepsi?	1	2	3	4	5	*97*

		Ja, så mye jeg ville	Ja, for en stor del	Ja, delvis	Ja, litt	Nei, ikke i det hele tatt	
86.	I løpet av **de siste 4 ukene**, var noen tilgjengelig for å hjelpe deg om du trengte og ønsket hjelp?	1	2	3	4	5	*98*

		Hele tiden tiden	Det meste av tiden	En stor del av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt	
87.	Hvor mye av tiden **de siste 4 ukene** har du følt deg forbigått?	1	2	3	4	5	6	*99*

		Alltid	Svært ofte	Ganske ofte	Av og til	Nesten aldri	Aldri	
88.	I løpet av **de siste 4 ukene**, hvor ofte har du følt deg isolert fra andre?	1	2	3	4	5	6	*100*

89. Hvor god eller dårlig synes du din helse er? På termometer-skalaen nedenfor er den best tenkelige helsetilstanden 100 og den verst tenkelige tilstanden 0. Vennligst vis hvordan du føler at din helse er ved å sette ring rundt ett tall på skalaen. **Ta med din epilepsi som en del av din helse når du besvarer dette spørsmålet.**



101-103

The following errors have been corrected in the Thesis after it was approved for defence and before printing

Abbreviations for types of corrections:

Cor – correction of language

Cpltf – change of page layout or text format

Page	Line	Original text	Type of change	Corrected text
17	17	developing to …	Corr	developing into …
26			Cpltf	Blank page removed
46	21	…menstrual disturbances.	Corr	…menstrual disturbances (28).
56	2 - 3	ATP-dependent K^{+-} channels	Corr	ATP-dependent K^{+}- channels
77	5	intern validity	Corr	internal validity

Errors in the printed version of Paper 3:

Page	Column	Line	Original text	Type of change	Corrected text
5	1	12	-4 kg (95% CI; -6-2, p<0.001)	Corr	-4 kg (95% CI; -6--2, p<0.001)
6	2	2	16% (95% CI; -8-23)	Corr	16% (95% CI; -8--23)

Also in Paper 3: in Tables 3 and 4 below, the corrections (hyphens) are highlighted:

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

	Diet group (n=21-24)[1]	**Control group (n=29-32)**[1]	**Inter-group comparison after 12 weeks intervention**	
	Baseline Mean (95% CI)	Baseline Mean (95% CI)	Difference[2] (Mean 95% CI)	p-value
ASAT, mmol/L	19.1 (16.1-22.3)	20.1 (17.9-22.3)	1.5 (-2.6-5.7)	0.47
ALAT, mmol/L	29.2 (21.7-36.7)	25.9 (21.1-30.7)	2.5 (-3.8-8.8)	0.43
Carnitine free, mmol/L	37.8 (32.5-43.0)	31.4 (27.5-35.2)	-8.9 (-13.4--4.4)	<0.001
Carnitine total, mmol/L	48.8 (43.3-54.3)	41.8 (37.1-46.5)	-5.4 (-10.5--0.3)	0.04
Uric acid, µmol/L[3]	249 (210-289)	243 (218-268)	20 (-2-42)	0.08
HbA1c, %	5.3 (5.0-5.5)	5.3 (5.2-5.4)	-0.2 (-0.4--0.1)	0.009
Total cholesterol, mmol/L	5.2 (4.7-5.7)	5.3 (4.9-5.7)	0.6 (0.1-1.1)	0.01
LDL cholesterol, mmol/L	3.1 (2.6-3.5)	3.2 (2.8-3.6)	0.8 (0.3-1.2)	0.001
HDL cholesterol, mmol/L	1.7 (1.5-2.0)	1.6 (1.5-1.8)	-0.0 (-0.1-0.1)	0.95
Triglycerides, mmol/L[4]	0.8 (0.6-1.2)	0.9 (0.6-1.5)	0.0 (-0.1-0.2) [4]	0.75

[1] The variation in n is due to missing data.

[2] Difference between the groups at the end of the 12 week intervention period (diet versus control), adjusted for baseline values by analysis of covariance.

[3] Reference 230-480 µmol/L

[4] Due to skewed data we present the medians with inter quartile range at baseline. Triglyceride data was transformed with natural logarithm in the analysis of covariance.

[5] Hodges-Lehman estimate of difference in the medians of the two groups (diet versus control) with 95% CI.

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

	Diet group		Control group		Inter-group comparison	
	Before intervention Mean (95% CI) µmol/L	Per cent change Mean (95% CI) %	Before intervention Mean (95% CI) µmol/L	Per cent change Mean (95% CI) %	Difference Mean (95% CI) µmol/L	p-value
CBZ	n=4 35.6 (28.9-42.4)	n=4 -31.0 (-49.6--12.5)	n=7 35.4 (28.6-42.2)	n=7 7.6 (-15.6-30.7)	-13.2 (-22.9--3.5)	0.014
ZNS	n=2 71.5 (56.3-86.7)	n=2 -35.4 (-111.4-40.5)	n=3 90.4 (-26.0-206.7)	n=3 -10.3 (-77.0-56.4)	-16.7 (-90.2-56.8)	0.43
LEV	n=5 71.8 (34.7-108.9)	n=5 10.5 (0.1-20.9)	n=8 100.8 (51.3-150.2)	n=8 -0.3 (-15.8-15.2)	8.3 (-6.2-22.7)	0.23
VPA	n=6 495.7 (424.4-567.0)	n=6 -18.4 (-36.6--0.2)	n=10 453.0 (303.8-602.2)	n=10 -4.2 (-14.7-6.2)	-61.4 (-131.0-8.2)	0.08
TPM	n=5 27.5 (20.5-34.5)	n=5 -12.0 (-38.0-13.9)	n=3 24.2 (2.2-46.2)	n=3 7.6 (-44.6-59.7)	-3.6 (-11.9-4.8)	0.32
OXC	n=8 85.8 (71.6-99.9)	n=8 -6.1 (-20.6-8.5)	n=10 83.4 (60.5-106.3)	n=10 3.5 (-6.6-13.7)	-7.2 (-21.5-7.2)	0.30
CLB[1]	n=3 5.9 (-3.0-14.8)	n=3 -26.1 (-43.4--8.8)	n=5 3.9 (0.9-6.8)	n=5 -0.6 (-13.5-12.4)	-1.3 (-2.5--0.1)	0.035
LTG	n=8 26.9 (16.5-37.2)	n=8 -9.7 (-21.9-2.4)	n=5 38.3 (25.1-51.5)	n=5 2.6 (-6.9-12.1)	-4.7 (-10.6-1.1)	0.10
LCM	n=3 16.3 (2.7-30.0)	n=3 -19.5 (-47.2-8.2)	n=1 19.0	n=1 31.6	--	--
PGB	n=0	--	n=2 15 (2.3-27.7)	n=2 20.5 (-81.6-122.6)	--	--
CZP	n=1 25	n=1 -36	n=1 72	n=1 -4.2	--	--
PB	n=0	--	n=2 30.5 (-141.0-202.0)	n=2 -2.5 (-120.5-115.6)	--	--
PHT	n=1 40	n=1 -12.5	n=2 52 (13.9-90.1)	n=2 -6.3 (-111.6-99.1)	--	--

CBZ=carbamazepine, ZNS= zonisamid, LEV=levetiracetam, VPA=valproate, TPM=topiramate, OXC=oxcarbazepine, CLB= clobazam, LTG=lamotrigine, LCM=lacosamid, PGB=pregabalin, CZP=clonazepam, PB=phenobarbital, PHT=phenytoin

[1] Desmethylclobazam