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

Doctoral thesis by

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ACKNOWLEDGEMENTS

The present work was carried out at the National Centre for Epilepsy, Division of Clinical Neuroscience at Oslo University Hospital in the period 2011-19.

My interest in dietary treatment of epilepsy started during a temporary position at the children’s department of the National Centre for Epilepsy in 2009-10. In 2010 the possibility of an adult research project emerged and was encouraged by Rasmus Lossius, Anette Ramm-Pettersen, Grete Almåsbak and Karl Otto Nakken, management of the National Centre for Epilepsy at that time. Thanks for giving me the opportunity.

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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.


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


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 to 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.

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

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

*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

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

*Comparing change of mean seizure frequency in both groups*
1.3.1 Several variants of the diet

Today, several variants of KD 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

<table>
<thead>
<tr>
<th>1. Classical ketogenic diet (CKD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Medium Chain Triglyceride (MCT) diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Modified ketogenic (Atkins) diet (MKD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Low-glycaemic-index treatment (LGIT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 &lt; 50.</td>
</tr>
</tbody>
</table>

\(^a\) 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.
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 KD 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 (\textit{KCNJ11} and \textit{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, \textit{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 within 12 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. 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 KD treatment 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). KD treatment 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 KD treatment 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 KD treatment is highly variable. However, some patients suffering from several of these syndromes respond extremely well to KD treatment (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 C₈ and C₁₀ (179). Recently, a direct antiepileptic action of decanoic acid (C₁₀) 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 C₁₀ 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 KD (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 KD (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 weak 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.

![Diagram showing study arms and point of time for data collection.](image)

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

<table>
<thead>
<tr>
<th>% seizure reduction</th>
<th>Diet group (n=28)</th>
<th>Control group (n=34)</th>
<th>Relative Risk (95% confidence interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>3 (11%)</td>
<td>2 (6%)</td>
<td>1.8 (0.3-10.2)¹</td>
<td>p=0.65¹</td>
</tr>
<tr>
<td>&gt;25</td>
<td>10 (36%)</td>
<td>5 (15%)</td>
<td>2.43 (0.94-6.28)²</td>
<td>p=0.06²</td>
</tr>
<tr>
<td>≤25</td>
<td>18 (64%)</td>
<td>29 (85%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

On-treatment analysis

<table>
<thead>
<tr>
<th>% seizure reduction</th>
<th>Diet group (n=24)</th>
<th>Control group (n=32)</th>
<th>Relative Risk (95% confidence interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>3 (13%)</td>
<td>2 (6%)</td>
<td></td>
<td>n.s</td>
</tr>
<tr>
<td>&gt;25</td>
<td>10 (42%)</td>
<td>5 (16%)</td>
<td>2.67 (1.05-6.79)²</td>
<td>p=0.03²</td>
</tr>
<tr>
<td>≤25</td>
<td>14 (58%)</td>
<td>27 (84%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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≤p≤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).

![Blood ketosis morning](image1.png) ![Blood ketosis evening](image2.png)

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 overestimated.

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 intern 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 loge 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.
References


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PAPERS I - IV