The Ketogenic Diet all Grown Up – Ketogenic Diet Therapies for adults

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Special issue: VSI: Ketogenic Dietary Therapy

Manuscript word count: 4393

Abstract word count: 159

Disclosures:

KSH: none

MCC:

Dr. Cervenka receives grants from Nutricia, Vitaflo, BrightFocus Foundation, and Army Research Laboratory. Honoraria from American Epilepsy Society, The Neurology Center, Epigenix, LivaNova, and Nutricia. Royalties from Demos. Consulting for Nutricia, Sage Therapeutics.

Abstract:

The use of ketogenic diet therapies (KDT) in adults has expanded in the last two decades and has been accompanied by a surge of new retrospective as well as prospective studies evaluating its efficacy in adults with epilepsy. In this review article, we will highlight the recent clinical trials and advances in the use of the ketogenic diet therapy (KDT) in adult patients with epilepsy. We will analyze the responder rate in regard to the epilepsy syndrome (focal vs generalized) to identify adults who are optimal to consider for KDT. In addition to its role in treating patients with chronic epilepsy, we will explore the emerging use of the KDT in the critical care setting in adults with refractory and super-refractory status epilepticus as well as other neurologic disorders. Finally, we will discuss special considerations for the use of KDT in adults with epilepsy including its potential long-term effects on bone and cardiovascular health, and its use in pregnancy.

Highlights:

- Three randomized controlled trials and several new observational studies demonstrated efficacy of a ketogenic diet therapy (KDT) in adult patients with epilepsy.
- KDT might have a potential benefit in New-Onset Refractory Status Epilepticus (NORSE).

The long-term effects of KDT on bone health, cardiovascular disease risk and its use in pregnancy remain uncertain.

1. Introduction

Almost one third of patients with epilepsy continue to have disabling seizures despite treatment with anti-seizure drugs (ASD) (Kwan and Brodie, 2000). In a recent study, only 2.1% of patients achieved optimal seizure control after trying a third ASD (Chen et al., 2018). Recent randomized clinical drug trials of newer ASDs report the responder rate (≥ 50% seizure reduction) compared to placebo as the metric for successful treatment (Ben-Menachem et al., 2016; Krauss et al., 2020). As an example a recent pooled analysis of three large clinical trials using brivaracetam showed a 40% responder rate, which has been consistent with many new ASDs (Ben-Menachem et al., 2016). Resective surgical intervention remains the best option for patients with intractable focal epilepsy when feasible (Wiebe et al., 2001). However, in a proportion of intractable epilepsy patients, resective surgery might not be an option (for generalized seizure disorders, when seizures localize to eloquent cortex, are multi-focal or patients prefer less invasive approaches). Over the past 1-2 decades, ketogenic diet therapies (KDT) emerged as a feasible therapeutic option for adult patients with intractable epilepsy (Felton and Cervenka, 2015). Moreover, there is more evidence that these diets have greater benefit in certain epilepsy syndromes (Kossoff et al., 2018).

Ketogenic diets therapies are characterized by a reduction in carbohydrate intake along with a relative increase in the proportions of fat and protein with the intent of promoting fat metabolism (McDonald and Cervenka, 2018b). When the classic ketogenic diet (CKD) was introduced in the 1920s as an alternative to fasting to reduce seizures, it was initially studied and utilized for both adults and children with epilepsy. In fact, one of the earliest large case series of 100 adolescents and adults reported a 56% seizure reduction in adult patients with the ketogenic diet (Barborka, 1930). As the era of anti-seizure medications emerged, the use of the ketogenic diet gradually declined in both the adult and the pediatric populations. In the mid-1990s, the use

of the CKD made a comeback for the treatment of intractable childhood epilepsies (Freeman et al., 1998; Kinsman et al., 1992; Swink et al., 1997). However, the resurgence of CKD in the treatment of adult patients with epilepsy did not begin until several years later (McDonald and Cervenka, 2017, 2018a).

Recently, there has been an exponential increase in the use of KDT in adults for intractable epilepsy. This has coupled with a surge of evidence assessing its use in adults with various neurological diseases (McDonald and Cervenka, 2019). Three randomized clinical trials and several observational studies evaluated the use of KDT in adults with epilepsy (Kverneland et al., 2018; McDonald et al., 2018a; Zare et al., 2017). Several case series reported a favorable use of the ketogenic diet in New-Onset Refractory Status Epilepticus (NORSE) and its subset Febrile Infection-Related Epilepsy Syndrome (FIRES) (Cervenka et al., 2017; Gugger et al., 2019; Williams and Cervenka, 2017). Preliminary data suggests some benefits of the ketogenic diet in patients with malignant glioma (Rieger et al., 2014), Alzheimer's disease (Brandt et al., 2019; Krikorian et al., 2012), and chronic headaches (Di Lorenzo et al., 2018) among others.

In this review article, we will explore the recent advances and clinical trials providing evidence to support the use of the ketogenic diet therapies in adults with epilepsy with special emphasis on the use of KDT in refractory status epilepticus.

2. Types of KDTs used in adults

There are 5 types of KDT used in adults (Kossoff et al., 2018). The classic ketogenic diet (CKD) is composed of a 4:1 ratio (4 grams of fat to every 1 g of protein plus carbohydrate combined) (Cervenka and Kossoff, 2013). The Medium Chain Triglyceride oil Ketogenic Diet (MCT KD) integrates medium-chain triglyceride oil as a diet supplement where 40-60% of the

energy consumption is supplied by MCT oil (Neal et al., 2009). This allows for a greater carbohydrate and protein intake while maintaining a metabolic state in which the body continues to produce ketones (45% fat, 20% protein and 35% carbohydrates) (Neal et al., 2009)

The modified Atkins diet (MAD) is typically composed of a net 10–20g/day carbohydrate limit (most often 15-20 grams in adults), which is equivalent to a ratio of 1 – 2 : 1 of fat to protein and carbohydrates combined (Kossoff et al., 2003). The low glycemic index treatment (LGIT) consists of 40 – 60 g daily of carbohydrates with glycemic indices less than 50 (contributing to 10% of total caloric intake) with approximately 60% of dietary energy derived from fat, 30% from protein and is less often used in adults (Muzykewicz et al., 2009; Pfeifer et al., 2008). A hybrid between the CKD and MAD is called a Modified Ketogenic Diet (MKD) where carbohydrate provides around 5% of the energy supply (approximately 20-30g) and fat provides about 75% (Martin-McGill et al., 2017; Roehl et al., 2019).

3. Efficacy of the KDT in the treatment of adult epilepsy

3.1 Effects of the KDT on seizure frequency

There has been a growing interest in the use of KDT in adult patients with epilepsy with a few randomized control trials (RCT) and several recent observational trials (Green et al., 2020; Kverneland et al., 2018; Zare et al., 2017). Overall, the rate of response (defined as ≥ 50% seizure reduction) ranged from 17% to 60% depending on the study. In this review article, we will emphasize the most recent trials in detail.

A randomized control trial in Iran evaluated the response rate of 34 patients after 2 months on MAD as an adjunct to ASDs compared to a control group of 32 patients whose ASD doses were also unchanged with habitual diet. Inclusion criteria included adult patients (age ≥

18) with drug-resistant epilepsy. Notable exclusion criteria included patients who had either an episode of status epilepticus or had a 2 week seizure-free period within the 6 months prior to enrollment. In the treatment arm, 18 patients had focal epilepsy and 16 patients had generalized epilepsy. Twelve patients in the treatment arm (35%) dropped out of the study due to non-compliance with the diet. Based on an intention-to-treat analysis at 2 months, 35.5% (12/34) were responders. None of the patients achieved seizure freedom and the response to MAD with respect to epilepsy type was not reported (Zare et al., 2017).

Another RCT from Norway compared the change in seizure frequency in patients with drug-resistant focal epilepsy. Patients were older than 16 years, had either focal or multifocal epilepsy with at least 3 countable seizures per month, and had tried at least 3 ASDs (including current treatment). Notable exclusion criteria included change in anti-seizure medications, episode of status epilepticus in the preceding 6 months, and having undergone resective surgery or vagal nerve stimulator implantation during the preceding 12 months prior to the trial. Initially, 37 patient were randomized to the MAD group and 38 patients to the control group. However, 28 patients started MAD compared to 35 patients on habitual diet, both combined with stable doses of ASDs. Four patients in the MAD group dropped out (three due to worsening seizures and one due to non-compliance) (Kverneland et al., 2018). There was no difference in the proportion of responders between the two arms, but the diet group had a significant moderate benefit (25-50% seizure reduction) (Kverneland et al., 2018).

McDonald et al evaluated whether the use of a ketogenic formula (KetoCal®) during the first month of MAD improves seizure reduction. Patients were $\geq$ 18 years with at least 4 quantifiable seizures per month who failed a trial of $\geq$ 2 ASDs at maximum doses. Out of the 80 patients who were initially randomized, 65 (81%) had focal epilepsy while 15 (19%) had

generalized epilepsy. Six patients elected not to start the diet, 5 were lost to follow-up by 1 month, 3 were non-compliant with the diet, 4 patients were non-compliant with the intervention (KetoCal®), and additional 6 patients were excluded from the analysis due to either ASD changes or failure to keep a seizure diary (McDonald et al., 2018a). Using an intention-to-treat analysis at 1 month, 30 patients (37.5%) achieved ≥ 50% seizure reduction, compared to 23 patients (29%) at 2 months and 20 patients (25%) at 6 months (McDonald et al., 2018a). Supplementing MAD with a ketogenic formula did not result in a difference in the responder rate, however, it seemed to improve compliance as significantly more adults remained on MAD long-term in the treatment arm (McDonald et al., 2018a).

The most recent study was a prospective observational study from the UK. Green et al evaluated the responder rate to the Modified Ketogenic Diet (MKD) in 40 patients, 26 of them with focal epilepsy and 14 with generalized (Green et al., 2020). The diet efficacy was assessed at regular 3-month intervals up to 12 months. Of the whole cohort, 5 patients (12.5%) attained a period of seizure freedom (defined as a period of freedom from all types of seizures for three-times the longest pre-diet interval between seizures) while 15 patients (38%) had ≥ 50% seizure reduction (Green et al., 2020). However, the retention rates were 60% at 3 months, 43% at 6 months, and only 29% at 12 months (Green et al., 2020).

Two meta-analyses addressing the efficacy of the KDT in adults have been published. A meta-analysis reviewing observational studies of KDT in adults showed a combined rate of seizure freedom of 13% and 53% responder rate (Liu et al., 2018). This was based on the results of 16 studies including 338 patients (5 studies using KD, 8 studies using MAD, 1 using both MAD/KD, 1 each using low-glycemic index diet and low-dose fish oil diet) (Liu et al., 2018). In another meta-analysis published in 2015, evaluating 12 studies, the responder rate ranged from

13-70% (Ye et al., 2015). The authors separated their analyses according to the type of KDT, with a combined responder rate of 52% for the CKD and 34% for the MAD (Ye et al., 2015).

3.2 Effects of the KDT on seizure severity and quality of life

Besides effect on seizure frequency, patients on a KDT also reported an overall decrease in the seizure severity (Kverneland et al., 2018; Schoeler et al., 2014) along with an improvement in mood, energy and overall quality of life (Lambrechts et al., 2013; Lambrechts et al., 2012; Schoeler et al., 2014). In the 2018 RCT from Norway, 29% of patients in the diet group had a clinically relevant score reduction on the Liverpool Seizure Severity Scale compared to only 6% in the control group (Kverneland et al., 2018). Roehl et al reported a 76% improvement in the seizure severity (based on patient reporting) and an 87% improvement in overall quality of life when assessed at a 3-month follow up (Roehl et al., 2019). Moreover, 78% of the patients reported weight loss. Patients who had improvement in seizure severity lost more weight when compared to those who had no improvement in their seizure severity (Roehl et al., 2019).

3.3 Efficay of the KDT based on epilepsy syndrome

Whether all types of seizures respond equally to a KDT remains unknown (Schoeler et al., 2013). In children, KDT has greater benefits in the treatment of certain epilepsy syndromes, such as Dravet syndrome, epilepsy with myoclonic-atonic seizures, mitochondrial disease, and Febrile Infection Related Epilepsy Syndrome or FIRES (Kossoff et al., 2018; Nangia et al., 2012). Historically in adults, KDT was thought to be more beneficial in generalized compared to focal epilepsy syndromes (Klein et al., 2010; Nei et al., 2014). However, more recent trials in

patients with focal epilepsy reported comparable results (Kverneland et al., 2018). In the study by Green et al, there was no difference in the responder rate between focal vs generalized epilepsy syndromes (38.5% vs 35.7%, respectively)(Green et al., 2020). Moreover, there was no difference in the response rate based on the brain imaging finding in a recent study (Falco-Walter et al., 2019).

In an attempt to elucidate whether there is any difference in the response to KDT between the two types of epilepsy, we reviewed all the studies in adult patients evaluating KDT and analyzed the response according the epilepsy type (focal vs generalized) when the distinction was made (Table 1). Twenty-one prospective and retrospective studies were identified. Although most studies reported epilepsy type (focal vs generalized) in the patients' demographics, not all of them separated response to the KDT by epilepsy type (Table 1). Ten studies included generalized as well as focal epilepsy syndromes in their cohort and response according to the type of epilepsy was either stated or could be inferred based on the data provided, 3 studies included only patients with focal epilepsy, while 2 studies evaluated patients with only generalized epilepsy. In the remaining 6 studies, the responder rate according to the epilepsy type was not mentioned. Using an intention-to-treat analysis and pooling all twenty studies, 687 adult patients with epilepsy had tried KDT. Average responder rate (≥50% seizure reduction) was 38% with approximately 12% of patients achieving a period (ranging from 1 to 24 months) of >90% seizure reduction or seizure freedom. Sixty-six out of 197 patients (34%) with focal epilepsy were responders (data from 13 studies), compared to 41 out of 86 patients (48%) with generalized epilepsy (data from 11 studies). Although the data are from different studies with different diets, different durations, some were retrospective and some were prospective, chi-square analysis shows a higher percentage of responder to the KDT in patients with generalized epilepsy (p 0.02).

3.4 Concomitant use of the KDT and other treatments for intractable epilepsy

There is paucity of literature evaluating the combined use of KDT and other therapies for adult patients with epilepsy. In children, the KDT seems to have a synergistic effect with zonisamide and with vagal nerve stimulation (VNS) (Kossoff et al., 2007; Morrison et al., 2009). Falco-Walter et al analyzed the effects of KDT in subgroup of adult patients with prior resective surgeries and VNS (Falco-Walter et al., 2019). A 56% response rate was achieved in 16 patients (29% of the cohort) with prior surgical intervention, and a similar 53% response rate in 19 patients (35% of the cohort) with a VNS (Falco-Walter et al., 2019). Whether there was a synergistic effect between the KDT and VNS was not evaluated in this study.

4. Super-refractory status epilepticus (SRSE) and New Onset Refractory Status Epilepticus (NORSE)

Refractory status epilepticus (RSE) is defined as SE persisting despite the administration of at least two parenteral anti-seizure drugs including an appropriately-dosed benzodiazepine. Super-refractory SE (SRSE) is defined as SE persisting at least 24 hours after onset of anesthesia, either without interruption despite appropriate treatment with anesthesia, recurring while on appropriate anesthetic treatment, or recurring after withdrawal of anesthesia and requiring anesthetic reintroduction (Hirsch et al., 2018; Trinka et al., 2015).

About 15 to 22.6 % of cases of SE progress to RSE (Kapur et al., 2019; Novy et al., 2010). Of those, another 22% continue to progress to SRSE (Kantanen et al., 2015). Several lines of therapies have been tried over the years, and RSE and SRSE continue to carry high rates of morbidity and mortality (Ferlisi and Shorvon, 2012). The classic ketogenic diet provides a

promising avenue for the treatment of RSE and SRSE, particularly because it can be administered as a formula via nasogastric tube in an emergent setting (Williams and Cervenka, 2017). The CKD has a relatively quick onset, has been shown to be feasible to administer in the intensive care unit (Cervenka et al., 2017; Francis et al., 2019), and lacks the hemodynamic adverse effects seen with high dose anesthetics (Williams and Cervenka, 2017).

The first published use of a ketogenic diet for SRSE in an adult was in France in 2008 (Bodenant et al., 2008). Subsequently, small case series utilizing a 4:1 CKD have been reported (Strzelczyk et al., 2013; Wusthoff et al., 2010). A case series of 10 adults with SRSE of median duration 21.5 days treated with a 3 to 4:1 ketogenic diet (9 with a 4:1 ratio KD and 1 with a 3:1 ratio KD) at 4 medical centers showed successful cessation of status epilepticus in all the patients who achieved ketosis (9 out of 10 adults) at a median of 3 days (range 1–31 days) (Thakur et al., 2014). In a large prospective multicenter study, 15 patients with SRSE received CKD after being in SRSE for a median of 10 days and trying a median of 8 ASDs. Fourteen patients completed the protocol and all achieved ketosis within 2 days. SRSE resolved in nearly ¾ of the patients (Cervenka et al., 2017). Francis et al reported 11 patients in whom the CKD was administered earlier (i.e. during RSE rather than SRSE)(Francis et al., 2019). SE ultimately resolved in all 11 patients, 8 patients during RSE while 3 patients progressed to SRSE prior to resolution (Francis et al., 2019). The authors postulated that an earlier use of a ketogenic diet might have minimized the risk of progressing into SRSE (Francis et al., 2019). As with most of the SE studies, it is challenging to delineate the sole effect of any single intervention on the outcome of SE given multiple simultaneous interventions are typically being performed in a critically ill patient.

Rarely, previously healthy patients without active epilepsy or other pre-existing relevant neurological disorders present with an explosive onset of refractory status epilepticus, named New Onset Refractory Status Epilepticus (NORSE)(Hirsch et al., 2018). This syndrome has been labelled with several acronyms in the past (Ismail and Kossoff, 2011), with a consensus expert definition being published more recently (Hirsch et al., 2018). Febrile Infection-Related Epilepsy Syndrome (FIRES) is a similar syndrome previously used mainly in the pediatric literature and is now classified as a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours prior to onset of refractory SE, with or without fever at onset of SE (Gaspard et al., 2018).

The pathophysiology of NORSE is not completely understood (Gaspard et al., 2018). van Baalen et al proposed an immune-mediated (with a complex inflammatory response) rather than an antibody mediated mechanism (van Baalen et al., 2017). An imbalance of the pro- and anti-inflammatory cytokine and chemokines has been suggested as a potential theory coupled with mitochondrial dysfunction (Gaspard et al., 2018). KDT has several theoretical benefits in the treatment of NORSE. Several animal studies have shown a decrease in the levels of proinflammatory cytokines and chemokines (IL-1, IL-6 and TNF- α) and/or a decrease in the CNS-derived CD4 cells with KDT (French et al., 2017). Moreover, the ketogenic diet has been associated with antioxidant effects (Maalouf et al., 2009) and may improve mitochondrial function by reducing the production of reactive oxygen species (ROS) (Milder et al., 2010).

In the 2018 NORSE consensus review article, the KDT had positive effects in 54% of patients with NORSE (19 out of 35 patients) and in 67% of patients with FIRES (8 out of 12 patients) (Gaspard et al., 2018). Park et al retrospectively reviewed 16 children with SRSE (10 of

which had FIRES) treated with KD (4:1 or 3:1 ratio), out of which 9 (56.3%) became seizure free and 6 (37.5%) had >50% seizure reduction. Subgroup analysis showed a higher number of responders to the KD in the FIRES group (Park et al., 2019). The most recent retrospective series was published from Johns Hopkins (Gugger et al., 2019) where 10 out of 20 NORSE patients received a 4:1 CKD. SE resolved in 7 patients (70 %) after initiation of KD; median time from initiation of KD to resolution of SE was 14 days (Gugger et al., 2019).

5. Compliance in adults to the KDT:

Compliance with an oral KDT in adults remains a challenge. Across several studies, the compliance of adults with KDT ranged between 38-62.9% (Green et al., 2020; Kossoff et al., 2008; McDonald et al., 2018a). Compliance rates are higher with MAD compared to CKD due to the less strict nature of the diet. In the meta-analysis by Ye el at, the compliance rate was approximately 45%, with higher compliance rates for MAD (56%) when compared to CKD (38%) (Ye et al., 2015). To our knowledge, there are no studies evaluating whether specific patient characteristics were associated with poor compliance. As discussed earlier, early supplementation with a ketogenic formula may improve compliance (McDonald et al., 2018a). Not surprisingly, experiencing an improvement in seizures significantly increases the likelihood of compliance and continuing KDT (Green et al., 2020).

6. Adverse effects:

The KDT has limited absolute contraindications in adults. Given the shift in energy metabolism to fat, the KDT is contraindicated in disorders of fatty acid oxidation and transport, porphyrias, liver failure, organic acidurias, and certain inborn errors of metabolism which are typically diagnosed in childhood (Kossoff et al., 2018).

The most common side effects of KDT in adults are gastrointestinal effects, weight loss, alterations in lipid profiles, and menstrual irregularity (Cervenka et al., 2016a; Sirven et al., 1999). Gastrointestinal effects include constipation more frequently than diarrhea unless MCT oil is being used for supplementation, nausea and vomiting and are all usually mild, can improve with time, and can often be managed with certain diet modifications. KDT may be associated with deficiencies in certain vitamins, trace elements such as zinc and selenium, and carnitine (Cervenka and Kossoff, 2013). Adults on KDT are typically recommended to take multivitamin including vitamin D, mineral, and calcium supplements (Cervenka and Kossoff, 2013). Weight loss is a positive side effect in many adults using KDT, while the use of KDT in patients with anorexia may be relatively contraindicated.

7. Special considerations in adults on KDT long-term:

7.1 Bone Health:

Chronic use of KDT in children has been associated with a decrease in bone mass and an increase in risk of fractures. In one study, there was a 0.16 standard deviation decrease in the bone mineral density (BMD) for every year the child remained on the KDT (Simm et al., 2017). The exact mechanism of how the KDT contributes to lower bone mineral density is not completely understood, but a high acid load from hyperketonemia, alteration in calcium and vitamin D, and lowering growth factors can all play a role (Bergqvist et al., 2008; Kossoff et al., 2018).

It remains unclear whether the KDT effects on bone health are different when used in adults. Three patients with Glucose Transporter Type 1 Deficiency Syndrome (G1 DS) treated with KDT for > 5 years had no change in their bone mineral content and bone mineral density

(Bertoli et al., 2014). In another study, 2 out of 11 (18%) adults screened with a bone mineral density scan had newly diagnosed osteopenia or osteoporosis (Cervenka et al., 2016b). The use of some enzyme-inducing ASDs may contribute to accelerated bone loss (Pack, 2003) in certain patients.

7.2 Lipids profiles and cardiovascular health

KDT may be associated with a transient alteration in the lipid profile along with a decrease in the body mass index (BMI). Serum cholesterol and low-density lipoprotein (LDL) have been shown to transiently increase followed by normalization (after 1 year) (Cervenka et al., 2016c). Longer term follow-up data is lacking in adults. Heussinger et al followed 10 patients with G1 DS treated with KDT. During the first 2 years, the total cholesterol, high-density lipoprotein (HDL), and LDL decreased while there was a mild increase in the mean triglycerides during the first 6-12 months (Heussinger et al., 2018). When measured at 5-10 years, all the values have returned to baseline (Heussinger et al., 2018). The same pattern was observed in the body mass index (BMI) with a transient increase for the first 2 years, followed by resolution of the difference with longer follow up (Heussinger et al., 2018). In another study with a mean follow up of 25 months, 20 patients treated with MAD had significantly lower triglyceride levels but increased levels of small dense LDL particles (a newer biomarker associated with increased cardiovascular risk) when compared to a control group not exposed to KDT (McDonald et al., 2018b). Measures of carotid intima media thickness (CIMT) were used as a collateral indicator of cardiovascular risk. In both studies, there was no difference in CIMT in patients on KDT when compared to controls (Heussinger et al., 2018; McDonald et al., 2018b). In an additional study, there was a significant

decrease in the serum HbA1C in patients treated with KDT measured at a 12-week period (Kverneland et al., 2018).

In a non-randomized open-label clinical trial in patients with type 2 diabetes mellitus, 262 patients received KDT and were compared to 87 controls (on standard diet) (Bhanpuri et al., 2018; Hallberg et al., 2018). The treatment group had significant decrease in mean HbA1C, weight loss, and an overall decrease in the insulin requirements and the dosages of other diabetes medication (Hallberg et al., 2018) . Moreover, there was an improvement in most biomarkers of cardiovascular risk after 1 year, including the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score and high sensitivity C-reactive protein (Bhanpuri et al., 2018).

7.3 KDT and pregnancy

In general, the use of KDT is not recommended in pregnant patients or women planning pregnancy. This stemmed from animal studies reporting altered embryonic organ growth, disturbed neuroanatomy and reduced brain volume (Sussman et al., 2013a; Sussman et al., 2015; Sussman et al., 2013b). However, it is uncertain whether the potential benefits from improved seizure control and potential reduction in ASDs prior to pregnancy in some patients would outweigh the theoretical risks of KDT to fetal health. There are 2 reported cases where patients became pregnant while on the KDT (van der Louw et al., 2017). In one patient, there were no developmental concerns by 12 months of age, while the other patient's offspring was born with bilateral ear deformities of unknown significance (van der Louw et al., 2017).

7.4 Effects of the KDT on ASD

There is inconsistent data regarding pharmacodynamic and pharmacokinetic interactions of the KDT with ASD (Coppola et al., 2010; Kverneland et al., 2015b). In a recent prospective study of 63 adult patients treated with MAD, there was a significant decrease in the serum concentration of ASD of 10.5% and 13.5% when measured at 4 and 12 weeks respectively (Kverneland et al., 2019). The greatest and the most consistent changes were in the serum concentrations of clobazam, carbamazepine and valproic acid (Kverneland et al., 2019). However, earlier data found no significant effect of KDT on the serum concentration of ASD, except valproic acid (Heo et al., 2017).

8. KDT in other neurological disorders

The use of KDT has expanded in the last decade to several other neurological disorders, including but not limited to gliomas (Klement et al., 2020; Martin-McGill et al., 2018; Rieger et al., 2014), Alzheimer's disease (Brandt et al., 2019; Krikorian et al., 2012), Parkinson's disease (Phillips et al., 2018), multiple sclerosis (Bahr et al., 2020; Choi et al., 2016), and primary headache disorders (Di Lorenzo et al., 2018).

Several small studies have shown some benefit (with a short term stable disease burden or partial response) of KDT in high grade glioma (Klement et al., 2020; Martin-McGill et al., 2018; Rieger et al., 2014). A small RCT utilizing MAD demonstrated an increase in the Memory Composite Score along with a subjective increased energy in 9 patients with mild cognitive impairment (Brandt et al., 2019). Similar results were seen in an earlier study where 23 patients with MCI were randomly assigned to either high carbohydrate or very low carbohydrate diet (Krikorian et al., 2012). In both studies, it appeared that the level of ketones produced correlated positively with memory performance (Brandt et al., 2019; Krikorian et al., 2012). In

patients with PD, there was an improvement in the non-motor symptoms on KDT (Phillips et al., 2018). A single RCT evaluated CKD in patients with multiple sclerosis and showed an improvement in the health-related quality of life and a mild reduction in the expanded disability scale status (EDSS)(Choi et al., 2016). A clinical trial is underway evaluating effects of the MKD on disease progression of MS (NCT03508414) (Bahr et al., 2020).

9. Conclusions and future directions:

Although the KDT has been used in the treatment of epilepsy for nearly one century, several questions remain unanswered and pose further exploration. It is clear that some adults with epilepsy achieve significant benefits while on the KDT. In the era of precision medicine, it is critical to identify ideal candidates for KDT (Table 2). For example, the KDT has been significantly beneficial in patients with G1DS, Angelman syndrome and Tuberous Sclerosis complex. Future studies are needed to explore the effectiveness of the KDT within specific epilepsy syndrome (focal vs generalized, structural vs genetic, etc.…). More unified KDT protocols and outcome measures across studies are encouraged (duration of follow up, percentage of seizure reduction, etc.…). Given the anti-inflammatory characteristics that the KDT possess (Forsythe et al., 2008), the potential use in autoimmune epilepsy and encephalitis is intriguing. Whether can we use KDT as a monotherapy or even earlier in the disease course remains unknown as well. Most of the patients enrolled in the trials had seizures that were refractory for several ASDs, and whether earlier use of KDT might be associated with better responder rate. Another important mechanistic consideration is whether the KDT could affect epileptogenesis (Lusardi et al., 2015; Todorova et al., 2000). Finally, the long-term effects of using KDT in adults remain uncertain, including but not limited to effects on bone health and

cardiovascular health, as well as other general medical conditions such as obesity, insulin resistance and the metabolic syndrome, and cognition.

Overall, positive evidence supports the use of ketogenic diet therapies in adults with intractable epilepsy and refractory status epilepticus, with expansion into the treatment of various neurological and non-neurological diseases in adults.

Acknowledgment: none

Table 1. Summary of all the studies evaluating KDT in adult patients with epilepsy (arranged in chronological order)

							Whole cohort		Focal		Generalized	
Study	Study type	Cohort Focal (F) Generalized (G)	Diet	Dropout	Reason for dropout	Dur (mo)	>90% sz (%)	> 50% sz (%)	>90% sz (%)	> 50% sz (%)	>90% sz (%)	> 50% sz (%)
Barborka 1930 (Barborka, 1930)	R	75 N/A	4:1 CKD	n/a	-	1-46	9/75 (12)	32/75 (43)	n/a	n/a	n/a	n/a
Sirven 1999 (Sirven et al., 1999)	R	11 F: 6 G: 5	4:1 CKD	4	C: 2 IE: 2	8	3/11 (27)	6/11 (55)	1/6 (17)	2/6 (33)	2/5(40)	1/5 (20)
Kossoff 2003 (Kossoff et al., 2003)	P	3 F: 3	MAD	0	-	3	0/3 (0)	1/3 (33)	0/3 (0)	1/3 (33)	-	-
Kossoff 2008 (Kossoff et al., 2008)	P	30 F: 23 G: 7	MAD	16	C: 7 IE: 9	3	1/30 (3)	13/30 (43)	n/a	11/23 (48)	n/a	3/7 (43)
Carette 2008 (Carrette et al., 2008)	P	8 F: 7 G:1	MAD	5	C: AE: 2 O: 2	6	0/8 (0)	1/8 (13)	0/7	1/7 (14)	0/1 (0)	0/1 (0)
Mosek 2009 (Mosek et al., 2009)	P	9 F:9	4:1 CKD	5	IE: 2 AE: 1 O: 2	2-3	0/9 (0)	2/9 (22)	0/9 (0)	2/9 (22)	-	-
Klein 2010 (Klein et al., 2010)	P	12 F: 7 G:5	3-4:1 CKD	5	C: 1 IE: 1 O: 3	4	1/12 (8)	5/12 (41)	0/7 (0)	2/7 (29)	1/5 (20)	3/5 (60)
Smith 2011 (Smith et al., 2011)	P	18 F: 16 G: 2	MAD	4	N/A	12	0/18 (0)	3/18 (17)	0/16 (0)	1/16 (6) (at least)	0/2 (0)	n/a
Coppola 2011 (Coppola et al., 2011)	R	6 F: 1 G: 5	LGIT	0	-	1-12	0 / 6	3/6 (50)	0/1 (0)	0/1 (0)	0/5 (0)	3/5 (60)
Lambrechts 2012 (Lambrechts et al., 2012)	P	15 F: 11 G: 4	MCT/KD	10	C: 1 IE: 8 AE: 1	12	0/15 (0)	2/15 (0)	0/11 (0)	2/11 (18)	0/4 (0)	0/4 (0)
Cervenka 2012 (Cervenka et al., 2012)	P	22 F: 13 G: 9	MAD	8	N/A	2	4/22 (18)	6/22 (27)	n/a	n/a	n/a	n/a

Kossoff 2013 (Kossoff et al., 2013)	R	8 G: 8	MAD	1	C: 1	-	4/8 (50)	6/8 (75%)	-	-	4/8 (50)	6/8 (75)
Schoeler 2014 (Schoeler et al., 2014)	R	23 F: 15[at least]	MAD & CKD 2 to 3:1	7	IE: 6 O: 1	12	2/23 (9)	9/23 (39)	n/a	n/a	n/a	n/a
Nei 2014 (Nei et al., 2014)	R	29 F: 11 G: 18	4:1 CKD	20	C: 11 IE: 9	24	1/29 (3)	14/29 (48)	n/a	3/11 (28)	n/a	11/18 (61)
Kverneland 2015 (Kverneland et al., 2015a)	P	13 G: 13	MAD	7	C: 5 WS: 1 O: 1	3	1/13 (8)	4/13 (31)	-	-	1/13 (8)	4/13 (31)
Cervenka 2016 (Cervenka et al., 2016a)	P	168 F: 110 G: 52	MAD>CKD	90	C: 34 IE: 18 AE: 5 O: 11 LF: 8	12	37/168 (27)	60/168 ()	N/A	N/A	N/A	N/A
Zare 2017 (Zare et al., 2017)	RCT	34 F: 18 G: 16	MAD	12	C: 12	2	0/34 (0)	12/34 (35)	n/a	n/a	n/a	n/a
Kverneland 2018 (Kverneland et al., 2018)	RCT	28 F: 28	MAD	4	C: 1 WS: 3	3	0/28 (0)	3/28 (11)	0/28 (0)	3/28 (11)	-	-
McDonald 2018	RCT	80 N/A	MAD	14	C: 9 LF: 5	1	n/a	30/80 (38)	n/a	n/a	n/a	n/a
Roehl 2019 (Roehl et al., 2019)	R	55 F:49 G: 6	mKD	0	-	3	n/a	33/55 (60%)	n/a	28/49 (57%)	n/a	5/6 (83%)
Green 2020 (Green et al., 2020)	P	40 F: 26 G: 14	mKD	28	C: 8 IE: 4 AE: 10 WS: 12	12	5/40 (13)	15/40 (38)	4/26 (15)	10/26 (39)	1/14 (7)	5/14 (36%)
TOTAL		**687** **F: 353** **G: 165**					**68/552[a] (12%)**	**260/687[b] (38%)**	**5/114[c] (4%)**	**66/197[d] (34%)**	**9/57[e] (16%)**	**41/86[f] (48%)**

a: based on data from 19 out of the 21 studies
b: based on data from all 21 studies
c: based on data from 10 out of the 21 studies
d: based on data from 13 out of the 21 studies
e: based on data from 9 out of the 21 studies
f: based on data from 11 out of the 21 studies

AE: adverse effects, O: other reasons, C: compliance, IE: ineffective , F: focal epilepsy, G: Generalized epilepsy, P: prospective, R: retrospective, RCT: randomized control trial, MAD: modified Atkins diet, mKD: modified Ketogenic diet, CKD: classic ketogenic diet, LGIT: low glycemic index treatment, MCT: Medium Chain Triglyceride Oil, WS: worsening seizures, LF: lost follow up

Table 2. Who could be an ideal adult candidate for KDT?

1- Patients with the following epilepsy syndromes:

Glucose transporter protein 1 (Glut-1) deficiency syndrome

Angelman syndrome*

Tuberous sclerosis complex*

2- Refractory generalized epilepsy patients (JME, JAE)

3- Drug-resistant focal epilepsy patients who are not surgical candidates

4- Drug-resistant focal epilepsy who failed surgical therapy

5- Patients with epilepsy who wish to limit ASDs due to side-effect burden

6- New onset refractory status epilepticus (NORSE) and other super-refractory status epilepticus

7 -Highly motivated and compliant patients and/or caregivers

* extrapolated from children.

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