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The evolving indications of KD therapy

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ABSTRACT

Despite the rapid increase of clinical and basic-science knowledge on ketogenic diet therapies over the past years, it has not always been easy to determine the adequate indications of this treatment. Over the nearly 100 years of use, from being a last resource in the therapeutic algorithm, the diet has become one of the four main treatments for patients with difficult-to-control epilepsy together with antiepileptic drugs, surgery, and vagus nerve stimulation. The use of the diet has also changed. The current paper will briefly discuss the history of the diet together with a review of the literature regarding its most important indications and how they have evolved.

The concept of the importance of defining the type of seizure, type of syndrome, and etiology in the selection of patients and timing of diet initiation has been gaining importance. This paper explores how the indications of the diet changed together with the shifting focus of epilepsy teams towards its use in different types of epilepsy and epilepsy syndromes and according to etiologies and as an alternative option in refractory and super-refractory status epilepticus.

1. Introduction

Despite the rapid increase of clinical and basic-science knowledge on ketogenic dietary therapies (**KDTs**) over the past years, it has not always been easy to determine the adequate indications of this treatment. In this review, we will see how in parallel with the development of the use of **KDTs**, the indications have evolved according to the different epilepsy syndromes, types of epilepsy, and age of the patients. The way of administration has changed as well. From being a last resource in the therapeutic algorithm, the diet has become one of the four treatments of choice for patients with difficult-to-control epilepsy together with antiepileptic drugs (AEDs), surgery, and vagus nerve stimulation.

In most studies mentioned in this article, the classic ketogenic diet was used, which we will here call the KD. Over the years, however, different alternative diets were developed to facilitate administration and improve palatability, such as the modified Atkins diet (MAD), the medium-chain triglyceride diet (MCT), and the low glycemic index treatment (LGIT), which together with the classic KD we will here call KDTs.

As the 100th anniversary of the diet is approaching, the aim of this study was to show how the indications of the diet have evolved over the last century. This article will briefly discuss the history of the diet together with a review of the literature regarding its most important indications.

2. The first indications of the diet

KDTs are currently considered an evidence-based treatment for refractory epilepsy; however, the use of the diet for this condition is not new. More than 2000 years ago, fasting was already considered to improve epileptic seizures. (Caraballo, 2017) Nevertheless, the first scientific evaluation of a diet for the treatment of epilepsy was in 1911 by two French physicians who started a calorie-restricted diet based on intermittent fasting in different patients with epilepsy claiming the diet worked well but was difficult to follow. (Höhn et al., 2019)

Some years later, Bernarr Macfadden, a fitness and health guru *avant la lettre* together with his assistant Dr. Conklin began to use periods of starvation to treat children with epilepsy. Simultaneously, Dr. H. Rawle Geyelin, an endocrinologist, also used fasting to treat epilepsy and was the first to publish his results on improvements both in seizures and cognitive functioning at the American Medical Association Convention in 1921. (Wheless et al., 2008) In the same year, Dr. Wilder at the Mayo Clinic postulated that a high-fat, low-carbohydrate diet could lead to ketosis mimicking fasting with the same antiseizure effect coining the term “ketogenic’. (Wheless et al., 2008) In 1925, his colleague Peterman developed the formula that is similar to the one used today. (Peterman, 1925). The diet became popular in the

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1920s and 30 s, (Höhn et al., 2019b) until, with the advent of the first antiepileptic drugs (AEDs), the KD started to be considered as difficult to maintain and obsolete. Only very few centers used the diet as a last resort in the treatment of refractory epilepsy.

In 1971, in an effort to make the classic KD more flexible and to increase its use, Dr. Peter Huttenlocher (1976) introduced a medium-chain triglyceride-oil diet, allowing more carbohydrates and thereby less restriction of food.

The diet became popular again after 1993, when Charlie Abrahams, a 2-year-old boy with intractable seizures, became seizure free on the diet at John Hopkins Hospital. His father, a Hollywood movie producer, created the Charlie Foundation to promote KD treatment and research. Since then, the KD has been increasingly used in the treatment of intractable epilepsy at an each time larger number of epilepsy centers (Kossoff and McGrogan, 2005; Henderson et al., 2006; Freeman et al., 2007). The KD became recognized as a last or next-to-last treatment option for most childhood epilepsies. Two international expert consensuses on the clinical management and indications of the diet have been published. (Kossoff et al., 2009, 2018).

3. Evolving indications

In spite of the new AEDs approximately one third of children with epilepsy remained drug resistant, resulting in renewed interest in the KD in the 1990s. Nevertheless, before 1998 there were no clear indications regarding the type of seizure or epileptic syndrome that best responded to the diet. In the first case reports of patients on the diet (Wilder, 1921; Peterman, 1925; Helmholz et al., 1927) only a general description of the indications was provided. (Höhn et al., 2019b)

Over the following years, however, epilepsy teams began to focus on the use of the KD in different types of epilepsy and syndromes as well as etiologies and started to apply it as alternative treatment in refractory (RSE) and superrefractory status epilepticus (SRSE). The concept of the importance of defining the type of seizure, type of syndrome, and etiology in the selection of patients and timing of diet initiation was gaining importance.

3.1. The use of the diet with a focus on the epileptic syndromes

After the first multicenter prospective study on the efficacy of the KD (Vining et al., 1998), publications evaluating which epileptic syndromes could benefit from the diet started to appear in the literature.

The KD was reported to be particularly useful in certain epilepsy syndromes (Nangia et al., 2012), especially the epileptic encephalopathies, such as epilepsy with myoclonic–atonic seizures (Doose syndrome) (Oguni, 2002; Laux and Blackford, 2004; Caraballo et al., 2005, 2006; Kilaru and Bergqvist, 2007), Dravet syndrome (Caraballo et al., 2005), infantile spasms (West syndrome) (Eun et al., 2006; Hong et al., 2010), and idiopatic Lennox-Gastaut syndrome (LGS) (Cross et al., 2012).

The first series on the efficacy of the KD in Dravet Syndrome (DS) was published in 2005 (Caraballo et al., 2005) describing a group of 42 patients with this type of epilepsy placed on the diet. Of these patients 75 % had a more than 50 % decrease in seizure frequency. In 2011 this cohort was updated (Caraballo et al., 2011a) and Nabbout et al. added evidence with a series of 15 patients with DS on the KD showing similar results (Nabbout et al., 2011). Two further retrospective studies supported these findings (Laux and Blackford, 2013; Dressler et al., 2015a,b) A recent prospective study by Yan et al., (Yan et al., 2018) evaluating 20 DS patients with *SCN1A* mutations on the KD has found a seizure reduction in 85 % and improvement in cognition in 80 %. A model of *SCN1A* mutant mice supported this evidence. Currently, KDTs are second line in the treatment algorithm for DS as outlined by the North American consensus panel (Wirrel et al., 2017; Cross et al., 2019).

In these years, similar evidence was found in patients with Doose syndrome or myoclonic astatic epilepsy (MAE). In 2002 Oguni (2002) analyzing 81 patients with MAE, stated that the KD was the most effective treatment for MAE, before ACTH and ethosuximide. During the following two years, similar evidence was provided by two different single-center studies. In 2006, in a prospective cohort of 11 patients with MAE treated with the KD, Caraballo et al. (2006) found that half the children showed a more than 50 % reduction in seizures while 18 % became seizure free. In 2007, Kilaru and Bergqvist (2007) described their clinical experience at the Children's Hospital of Philadelphia in subjects with MAE treated between 1998 and 2005. The treatment with the highest seizure freedom rate was the KD.

In 2001, Nordli et al. (2001) reported a retrospective series of 32 infants with infantile spasms (IS) treated with the KD who did particularly well on the diet. In a retrospective study published in 2008, Kossoff et al., 2008a,ba) compared the response of patients with new-onset IS treated with either the KD or ACTH as a first-line treatment. The authors postulated that the efficacy of the KD may be similar, but tolerance would be better than **ACTH. (**Gonzalez-Giraldo et al., 2018**)** Three prospective studies in children with IS on the KD showed a median efficacy rate of 65 % and a median seizure-free rate of 27.8 % (Hong et al., 2010; Lee et al., 2012; Pires et al., 2013**)**

In 2010 the Infantile Spasms Working Group stated that the KD may be considered as an option if ACTH and vigabatrin fail or are not indicated in a given patient. (Pellock et al., 2010) of three children with infantile spams without hypsarrhythmia that were placed on the KD, two responded well to the diet. (Caraballo et al., 2011a)

A little after the first decade of this century, evidence on the use of the KD in LGS was reported. In 2012, Lemmon et al. (2012) published a retrospective study of 71 children with LGS treated with the diet. They found that approximately one-half of children responded at 12 months. By that time, the diet had been successfully tried in LGS in different studies; however, further research was deemed necessary to determine the best timing and choice of diet. (Cross et al., 2012).

In 2014, Caraballo et al. published a series of patients with LGS, of whom 20 were placed on the diet. The KD was found to be effective and well tolerated not only for those with an unknown etiology but also for those with structural LGS. The authors recommended to use the diet early in the course of this syndrome. (Caraballo et al., 2014). Sharma et al. used the modified Atkins diet to treat children with LGS. In this study, adverse effects were mild and the diet was found to be effective and well tolerated. (Sharma et al., 2015)

The first Consensus on the Ketogenic Diet published in 2009 (Kossoff et al., 2009) highlighted the epilepsy syndromes and conditions in which KDTs had shown to be particularly beneficial. In the recent second Consensus the importance of the epileptic syndromes as well as etiologies was remarked (Kossoff et al., 2018).

Meanwhile, reports on the effect of the diet on other epileptic encephalopathies, such as epilepsy with focal migrating seizures in infancy, febrile infection-related epilepsy syndrome, or myclonic status in non-progressive encephalopathy, were published during this decade. (Caraballo, 2018)

Two case reports on infants with Ohtahara syndrome, a severe epileptic encephalopathy associated with intractable seizures and severe mental disability that may evolve to WS and LGS (Beal et al., 2012), were reported with good results (Ishii et al., 2011; Sivaraju et al., 2015). In a one-month-old male infant the seizures were brought under control on the diet, (Ishii et al., 2011) while in a 5 year-old child a substantial reduction in seizure frequency as well as clear behavioral improvement was observed. (Sivaraju et al., 2015)

Results of KD treatment in migrating partial seizures in infancy (MFSI) were variable. (Coppola, 2015) Three patients with MFSI refractory to AEDs with an onset before 5 months of age were put on the KD at our center. (Caraballo et al., 2015a) One became seizure free with significant improvement of neurocognitive function, the other had a 75-to-99 % seizure reduction with moderate psychomotor improvement, while the remaining patient had a less-than-50 % seizure reduction. In

all three patients tolerability was good.

Epilepsy with continuous spikes and waves during slow wave sleep (CSWS) or electrical status epilepticus during slow-wave sleep (ESES) is an epileptic encephalopathy of variable prognosis that is often drug resistant. Some patients develop steroid dependency. Nikanorova et al. (2009) evaluated the effect of the KD on electroclinical characteristics and cognitive function in five children with CSWS refractory to conventional AEDs. After 24 months on the KD, CSWS resolved in one patient, while a mild decrease in the spike-wave index was seen in one and lack of response in three patients.

Ville et al. (2015) found that in a consecutive series of 42 patients on oral steroids combined with the KD, of whom 13 had CSWS, eight responded well to the diet, concluding that patients with steroid-dependent CSWS seemed to be the best candidates for the diet.

In the same year, in a study by our group (Reyes et al., 2015) of 65 children with CSWS, 12 were placed on the KD as add-on to the use of one to three AEDs. The KD was effective regardless of etiology suggesting that the diet is a good treatment option for patients with CSWS, not only for structural cases but also for those with an unknown etiology.

All together, these results supported the concept that the KD may be introduced earlier in the treatment scheme of these patients.

3.2. The importance of the etiology in the indication of the ketogenic diet

The etiology of the different epileptic syndromes and/or types of epilepsy is crucial in the evaluation of treatment options, including KDTs. The importance of this concept when considering the diet as a therapeutic alternative for refractory epilepsy had become broadly accepted by 2008. These causes may be genetic (Yan et al., 2018), metabolic (Ramm-Pettersen et al., 2013), autoimmune (Nabbout et al., 2010; Peng et al., 2019), infectious (Caraballo et al., 2011c), as well as structural, both congenital (Park et al., 2018; Pasca et al., 2018) and acquired (Caraballo et al., 2011c). Around those years, surprising evidence appeared regarding the good response to KDTs of drug-resistant epilepsies secondary to specific etiologies.

In 2009, Thibert et al. (2009) reported on treatment options for epilepsy in patients with Angelman syndrome. In this series of patients, the KD was found to be successful. In a prospective study published in 2012 (Thibert et al., 2012), the same group evaluated a cohort of six children with Angelman syndrome who initiated the LGIT Pfeifer and Thiele, 2005 with good results, supported by a similar study by Grocott et al. (2017).

Previously, different studies on the efficacy of the KD according to etiology had been reported in small series of children with Rett syndrome (Liebhaber et al., 2003; Giampietro et al., 2006), Lafora disease (Cardinali et al., 2006), and tuberous sclerosis (Kossoff et al., 2005; Coppola et al., 2006; Kossoff et al., 2007; Martinez et al., 2007), the latter suggesting that the use of KDTs for more than two years may be beneficial for patients with tuberous sclerosis who have achieved seizure freedom. A decade later, Park et al. (2017) retrospectively reviewed 12 children with refractory epilepsy associated with tuberous sclerosis in which the KD improved cognition and behavior in addition to reducing seizure frequency.

Genetic diagnosis in epileptic encephalopathies is a recently introduced concept, as genetic etiologies may be associated with developmental delay regardless of the seizures. Among others, ion channel genes have been demonstrated to be implicated in severe epileptic encephalopaties.

Ko et al. in 2018, retrospectively evaluated the efficacy of ketogenic diet (KD) in 155 patients with developmental and epileptic encephalopathies associated with specific gene mutations. They found that patients with *SCN2A*, *STXBP1*, *KCNQ2*, and *SCN1A* mutations showed a better response to the KD, while those with *CDKL5* mutations showed a worse response. These findings are consistent with those of previous studies in patients with epileptic encephalopathy with *SCN1A* and *SCN2A* mutations. Patients with Ohtahara syndrome and *KCNQ2* or *STXBP1* mutations responded particularly well to the diet. (Ko et al., 2018)

The KD may also be an option for patients with inherited metabolic disorders (Caraballo, 2017). It is well-known that the diet is the treatment of choice for two distinct disorders of brain energy metabolism: Glucose transporter type 1 (GLUT-1) deficiency syndrome (Klepper and Leiendecker, 2007) and pyruvate dehydrogenase deficiency (PDHD) (Wexler et al., 1997). In both disorders, the KD provides ketones that bypass the metabolic defect and serve as an alternative fuel to the brain. (Scholl-Bürgi et al., 2015). Since first described in 1991, more than 300 patients with GLUT-1 deficiency syndrome have been reported. (De Vivo, 1991) Recently, the MAD was also shown to be effective in this group of patients. (Ito et al., 2011; Klepper and Leiendecker, 2013)

Already in 1976, the KD was shown to be beneficial in PDHD (Falk et al., 1976). Data to support the use of KDT in PDHD continued appearing in literature (Wexler et al., 1997), even if based on case reports. Recently, Sofou et al. has published a longitudinal cohort study of 19 children with PDHD in whom the KD was safe and effective for the majority of patients. (Sofou et al., 2017)

Different reports have suggested the use of KDTs in other metabolic disorders, mainly those of intermediary metabolism (glycogen storage diseases) (Bush et al., 2005; Brambilla et al., 2014) and disorders of mitochondrial energy supply, as the diet may cause specific changes in mitochondrial metabolism or function.

Clinical findings have indicated that the KD may control seizures in children with intractable epilepsy associated with mitochondrial respiratory chain complex defects (Kang et al., 2007; Lee et al., 2008), mitochondrial DNA depletion syndromes, such as Alpers-Huttenlocker syndrome (Khan et al., 2012), and disorders of mitochondrial transcription and translation (MELAS). (Steriade et al., 2014).

Early myoclonic encephalopathy (EME) is a syndrome with a poor prognosis and no effective therapy (Caraballo, 2018). Cusmai et al. reported three cases with neonatal nonketotic hyperglycinemia and EME. The KD in combination with AEDs led to a dramatic seizure reduction and improvement of quality of life. (Cusmai et al., 2012)

KDTs are also considered in inflammatory as well infectious etiologies regardless of the types of seizures and epilepsy or epileptic syndrome. In patients without a history of seizures who develop seizures that progress over a few days to status epilepticus, and in whom tumor, stroke, intoxication, vasculitis, and metabolic, infectious, or structural causes were ruled out, new-onset RSE (NORSE) should be suspected. (Hirsch et al., 2018) This is an important concept as it allows to take the diet into consideration as an add-on treatment option in an early stage of the disease. Febrile infection-related epilepsy syndrome (FIRES) is a subtype of NORSE that requires a febrile infection that started between 2 weeks and 24 h prior to the onset of RSE, with or without fever the at onset of the status epilepticus. (Hirsch et al., 2018) The first report of the use of the diet in FIRES was by Nabbout et al. (Nabbout et al., 2010). The authors evaluated nine patients with FIRES and refractory status epilepticus seen over 12 years. The KD worked in seven. In our series (Caraballo et al., 2013b) two of 12 children with FIRES with a mean follow-up of 6.5 years were put on the KD in the acute phase; one had a 50–75 % seizure reduction, while the other had a seizure reduction of less than 50 %. In 2014, Sing et al. reported good efficacy and improved cognitive function in two patients with FIRES on the KD. Status epilepticus resolved in both (Singh et al., 2014). Overall, these studies suggest the potential that KDTs may have in the treatment of FIRES. Better results are achieved when treatment is started early. In immune encephalitis associated with refractory epilepsy as well Rasmussen syndrome, KDTs may also be an option. (Caraballo et al., 2013a; Appavu et al., 2016)

There are reports of the KD being of benefit in refractory epilepsy due to focal lesions, such as hypothalamic hamartoma (HH). In 2011, Chapman et al. (2011) published a preliminary report suggesting that seizures associated with HH may respond well to the KD as ketone

Table 1
Overview of key studies of children with different epilepsy syndromes and electro-clinical patterns treated with KDTs.

Epileptic syndrome	First Author, year	Study design	Type KDTs
Epilepsy with Myoclonic-atonic seizures (Doose Syndrome)		*Retrospective*	*Classic KD*
	○ Oguni (2002)	*Retrospective*	*Classic KD*
	○ Laux and Blackford, (2004)	*Retrospective*	*Classic KD*
	○ Caraballo (2005, 2006)	*Retrospective*	*Classic KD*
	○ Kilaru and Bergqvist (2007)		
Dravet Syndrome		*Retrospective*	*Classic KD*
	○ Caraballo et al. (2005)	*Retrospective*	*Classic KD*
	○ Caraballo et al. (2011a)	*Prospective*	*Classic KD*
	○ Nabbout et al. (2011)	*Retrospective*	*Classic KD*
	○ Laux et al (2013)	*Retrospective*	*Classic KD*
	○ Dressler et al. 2015a,	*Prospective*	*Classic KD*
	○ Yan et al. (2018)		
Infantile Spasms		*Retrospective*	*Classic KD*
	○ Eun et al. (2006)	*Retrospective case-control vs ACTH*	*Classic KD*
	○ Kossoff et al., 2008a,b)	*Prospective*	*Classic KD*
	○ Hong et al. (2010)	*Retrospective*	*Classic KD*
	○ Lee et al. (2013)	*Prospective*	*Classic KD*
	○ Pires et al. (2013)	*Retrospective*	*Classic KD*
	○ Ville et al. (2015)		
Infantile spams without hypsarrhythmia	○ Caraballo et al. (2011b)	*Retrospective*	*Classic KD*
Lennox-Gastaut Syndrome	○ Lemmon et al. (2012)	*Retrospective*	*Classic KD*
	○ Cross et al. (2012)	*Retrospective*	*Classic KD*
	○ Caraballo et al. (2014)	*Retrospective*	*Classic KD*
	○ Sharma et al. (2015)	*Retrospective*	*Modified Atkins diet*
Othahara Syndrome		*Case report*	*Classic KD*
	○ Ishii et al. (2011)	*Case report*	*Classic KD*
	○ Sivaraju et al. (2015)	*Retrospective*	*Classic KD*
	○ Ko et al. (2018)		
Migrating partial seizures in infancy (MFSI)	○ Coppola (2015)	*Case report*	*Classic KD*
	○ Caraballo et al. (2015a)	*Case report*	*Classic KD*
Myoclonic status epilepticus	○ Caraballo et al. (2015b)	*Case report*	*Classic KD*
	○ Caraballo et al. (2017)	*Retrospective*	*Classic KD*
Continuous spike and wave during slow wave sleep (CSWS)	○ Nikanorova et al. (2009)	*Case report*	*Classic KD*
	○ Ville et al. (2015)	*Retrospective*	*Classic KD*
	○ Reyes et al. (2015)	*Retrospective*	*Classic KD*
FIRES	○ Nabbout et al. (2010)	*Case series*	*Classic KD*
	○ Caraballo et al. (2013b)	*Case series*	*Classic KD*
	○ Singh et al. (2014)	*Case series*	*Classic KD*
	○ Peng et al. (2019)	*Retrospective*	*Classic KD-EN and PKD*
		Case series	*Classic KD*
Rasmussen	○ Caraballo et al. (2013a)	*Case series*	*Classic KD*
	○ Appavu et al. (2016)		

Classic KD: classic Ketogenic diet.
EN: Enteral.
PKD: Parenteral Ketogenic Diet.
Modified KD: Modified Ketogenic Diet.
LGID: Low Glycemic Index Diet.
NS: non statement.

bodies might directly modulate the intrinsic epileptogenicity of HH tissue.

In 2012, Thammongkol et al. (2012) reported patients with lissencephaly and other malformations, including bilateral perisylvian polymicrogyria and hemispheric dysplasia, with a good response to the KD in agreement with a study on focal cortical dysplasia by Jung et al. (Jung et al., 2008). A good response was also seen in children with hypoxic-ischemic encephalopathy. (Thammongkol et al., 2012) In a recent study, Pasca et al. (2018) has shown effectiveness of the diet resulting in decreased seizure frequency and better quality of life in patients with drug-resistant epilepsy secondary to malformations of cortical development, although the authors also stated that seizure freedom is rarely achieved. The diet worked best in patients with unilateral or bilateral polymicrogyria, focal cortical dysplasia not amenable to surgery, and schizencephaly. (Pasca et al., 2018).

Overall, it is considered that children with a clear epileptogenic focus benefit more from resective surgery than from KDTs. (Stainman et al., 2007) However, KDTs may be used in combination with AEDs to reduce seizures as a bridge to surgery or in patients that are refractory to surgical treatment.

3.3. The use of the diet in status epilepticus

Over recent years, the diet has been increasingly used in refractory status epilepticus and super-refractory status epilepticus (RSE/SRSE) (Cervenka et al., 2011; Thakur et al., 2014; Wusthoff et al., 2014) both in children and in adults.

Analyzing the electroclinical experience in the use of KDTs for RSE, it was observed that children with refractory focal and less frequently generalized status epilepticus, primarily observed in focal epilepsies of different etiologies, respond particularly well to the diet. Other types of RSE with a good response to the diet are the pure form of myoclonic status epilepticus and non-convulsive and/or electrical status epilepticus in the context of the epileptic encephalopathies. (Caraballo, 2018, 2019)

The majority of the studies were conducted in patients with motor RSE associated with an immune-mediated etiology. Patients with focal non-convulsive RSE and generalized RSE have also been shown to respond well to the diet. (Thakur et al., 2014; Wusthoff et al., 2010; Cervenka et al., 2011; Kumada et al., 2010) A study on the use of the KD in myoclonic RSE showed a good response to the diet leading to a

Table 2
Overview of key studies of children with epilepsy of different etiologies treated with KDTs.

Etiologies & KDTs	First Author, year	Study design	Type KDTs
• Hypothalamic hamartoma	Chapman et al. (2011)	*Restrospective*	*Classic KD*
• Lissencephaly	Thammongkol et al. (2012)	*Prospective*	*Classic KD*
• Malformations of focal cortical dysplasia (bilateral perisylvian polymicrogyria and hemispheric dysplasia)	Jung et al. (2008)	*Retrospective*	*Classic KD*
	Pasca et al. (2018)	*Retrospective*	*Classic KD*
• Malformations of cortical development (abnormal post-migrational development)			
• GLUT 1 DEF	Klepper and Leiendecker (2007)	*Case series*	*Classic KD*
• PDHD	Ito et al. (2011)	*Case series*	*Modified Atkins diet*
• Mitochondrial disease	Falk et al. (1976)	*Case reports*	*Classic KD*
	Wexler et al. (1997)	*Case reports*	*Classic KD*
Complex 1	Sofou et al. (2017)	*Prospective*	*Classic KD*
Melas			
Alpers-Huttenlocker			
• Glucogenosis type V	Kang et al. (2007)	*Retrospective*	*Classic KD*
• Glucogenosis type III	Lee et al. (2008)	*Retrospective*	*Classic KD*
	Steriade et al. (2014)	*Case report*	*Modified KD*
	Khan et al. (2012)	*Case report*	*NS*
	Busch et al. (2005)	*Case report*	*Classic KD*
	Brambilla et al. (2014)	*Case report*	*Modified KD*
• Angelman	Thibert et al. (2009)	*Retrospective/ Survey*	*Classic KD- LGID*
• Rett	Thibert et al., 2012	*Prospective*	*LGID*
• Lafora Disease	Grocott et al. (2017)	*Retrospective*	*LGID*
• Tuberous Sclerosis	Liebhaber et al., (2003)	*Case report*	*Classic KD*
	Giampietro et al. (2006)	*Case report*	*Classic KD*
	Cardinali et al. (2006)	*Case report*	*Classic KD*
	• Kossoff et al. (2005)	*Retrospective*	*Classic KD*
	• Kossoff et al. (2007)	*Case Report*	*Classic KD*
	• Coppola et al. (2006)	*Case report*	*Classic KD*
	• Martinez et al. (2007)	*Retrospective*	*Classic KD*
	• Park et al. (2017)	*Retrospective*	*Classic KD and Modified Atkins diet*

decrease in ventilation time and number of AEDs. (Caraballo et al., 2017) Two studies evaluating patients with non-convulsive and/or electrical status epilepticus (ESES) treated with KDT found good results. (Reyes et al., 2015; Pasca et al., 2018)

Although in children with RSE and SRSE the effectiveness of KDTs may be difficult to evaluate due to the simultaneous use of other therapies (Peng et al., 2019), different pediatric series found a success rate of around 75 %. In responders the diet worked within 7–10 days. (Cervenka et al., 2011; Kossoff and Nabbout, 2013; Appavu et al., 2016; Arya et al., 2018)

The use of the diet for the emergency treatment of RSE and SRSE allows for control of the seizures and improvement of the general condition of the patient and may therefore also be used as underlying treatment or for short periods as a bridge to other therapies. (Caraballo et al., 2017) (Tables 1 and 2)

4. Age at diet initiation

4.1. The use of the diet in young children, infants, and neonates

For many years, the KD was not used in children under 2 years of age, as it was considered infants could not maintain ketosis. Additionally, the diet was deemed to be unsafe as growth requirements could not be met (Livingston, 1972). Nevertheless, in 2001 Nordli et al. (2001) retrospectively analyzed 32 infants younger than 2 years of age with different etiologies treated with the diet and found a 90 % response rate at 3 months while the diet was well tolerated. In 2015, a study from Austria retrospectively compared 58 infants younger than 1.5 years with older children and found that seizure control was better in the infants on the diet. (Dressler et al., 2015a,b) In the following year, Van der Louw et al. (2016) published the European guidelines for the use of KDTs in this age group.

Currently, there is good evidence to support the efficacy of KDTs in this age group and in specific syndromes. It has even been suggested that children younger than age 2 years are an ideal population in which to start the diet (Titre-Johnson et al., 2017). Recent case reports in neonates illustrate that KDTs are safe and effective even in infants as young as 6 weeks (Thompson et al., 2017) and that breastfeeding can be continued together with the ketogenic formula. (Le Pichon et al., 2019)

4.2. The use of the KD in adolescents and adults

Adolescents and adults were typically considered not to be candidates for KD treatment because of the unpalatability and strictness the diet, although several reports in this population were published (Barborka, 1930; Sirven et al., 1999; Mady et al., 2003; Kossoff et al., 2008a,b). Indeed, Wilder's first report was in adults placed on the KD. (Höhn et al., 2019b) In 1930, Barborka (1930) published data on a group of adult patients receiving the KD and not until much later did new studies in older patients appear in the literature. (Sirven et al., 1999; Mady et al., 2003; Mosek et al., 2009; Klein et al., 2010)

At the time of the first consensus guidelines, only 38 % of the consensus group offered dietary therapy to adults (Kossoff et al., 2018). Since then, however, there has been increased interest and research suggesting similar outcomes in the use of KDTs in adults. (Liu et al., 2018)

The different diet options, such as the MAD, the LGIT, and formulas, facilitate the use of KDTs in different age groups and different epilepsy syndromes and associated neurological conditions.

5. Timing of ketogenic diet therapy

In the past, the KD was used as a last resort after two or more AEDs had failed (Kossoff et al., 2018). Today, however, it is recommended to try the diet earlier in the treatment scheme, as approximately 25 % of the children with drug-resistant epilepsy responds to the diet immediately, some of them even during the initial fast. (Nabbout et al., 2011; Kossoff et al., 2008a,b).

As seen above, the diet may be indicated earlier in the treatment scheme of different epileptic syndromes. In addition, KDTs may be tried earlier in the course of RSE and SRSE secondary to certain etiologies and in emergency settings. (Caraballo, 2019).

6. Increased flexibility over time

Together with the changes in indications, the clinical management and administration of the diet have also evolved (Armeno et al., 2014). Where the early protocols were restrictive with prolonged fasting, today the diet is often started on an outpatient basis without the need for fasting, (Bergqvist et al., 2005; van der Louw et al., 2019) and while initially all foods had to be carefully weighed, currently there are KDTs with “free foods”, such as the MAD (Park et al., 2018) or formulas (Kossoff et al., 2004) and parenteral ketogenic solutions. (Armeno et al., 2019a, b)

The much feared adverse effects have proven to be largely preventable (Armeno et al., 2018), although there is still a gap in the knowledge regarding long-term complications, such as growth and cardiovascular alterations (Armeno et al., 2019a, b; Heussinger et al., 2018).

7. What will the future bring?

Almost a century has passed since the KD was first used in the treatment of epilepsy. Since then, other therapies have become available, such as new AEDs and vagus nerve stimulation. However, currently KDTs remain the most important non-pharmacological treatment for refractory epilepsy. It is now considered that KDTs should be used earlier in the treatment algorithm for several syndromes.

The diet has shown to be effective at certain ages and there is evidence it is the best treatment option for epilepsies with specific etiologies (Kossoff et al., 2018).

Adverse effects are now screened for, identified, and often prevented. There are four different types of KDT and two different ways of administration, enteral and parenteral, that have proven to be as safe and effective as food.

Specific issues that should be considered in the future are if KDTs may be used as first-line treatment and if a more simple diet initiation without fasting and on an outpatient basis is possible with the same effectiveness. The use of the diet is time consuming and considering the limited resources at many centers adequate identification of candidates is crucial. Additionally, greater flexibility in the use of the diet will make patients less dependent on the medical team. (Kossoff and Cervenka, 2019)

Further research, especially in the field of genetics, will be necessary for a better selection of candidates for the diet. (Ko et al., 2018; Caraballo, 2018) Another interesting topic to evaluate in the future are the patients with particular types of epileptic encephalopathies with a genetic etiology who may have an excellent response to KDTs. (Caraballo et al., 2007)

Finally, it is important to always keep in mind that the accurate indication of the diet is the key to success.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2020.106340.

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