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CRITICAL REVIEW AND INVITED COMMENTARY

The ketogenic and related diets in adolescents and adults—A review

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Summary

The ketogenic diet (KD) has been used to treat children with epilepsy who are resistant to antiepileptic drugs (AEDs) since the 1920s, and has undergone a resurgence in popularity over the last 15 years Its use in adolescents and adults has been more restrained. During the past few decades, more liberal regimens have emerged that may seem more attractive to older people while still proving effective, often independent of ketone levels. The KD and its variants may lead to similar reductions in seizure frequency in adolescents and adults as seen in children, although studies are limited and of poor quality. A total of only 122 adults and 82 adolescents have been included in open-label studies on the KD, and only 56 adults and 10 adolescents on the Modified Atkins Diet. Side effects appear similar to those encountered in children. Noncompliance may be higher in adolescents and adults than in children, but the main reason for discontinuation is lack of efficacy. A better understanding of the mechanisms underlying the effects of the KD might allow the same treatment effects to be achieved using novel, better-tolerated, nondietary approaches.

KEY WORDS: Epilepsy, Dietary treatment, Older people.

The ketogenic diet (KD) has been used since the 1920s for children with difficult-to-treat epilepsy, with resurgence in popularity during the past 15 years (Wheless, 2008). Use of the KD and its variants increased by 50% in the United Kingdom between 2000 and 2007 (Lord & Magrath, 2010), but dietary treatment is still rarely used in adults. Data on dietary treatments are published from >1,300 children <12 years of age, but from only 178 adults and 92 adolescents in open-label studies providing ages. An additional seven adults and one adolescent are included in case reports and series.

The KD can be an effective treatment option in children. Following preliminary reports concerning the effects of fasting on seizure cessation (Guelpa & Marie, 1911), a high-fat, low-carbohydrate diet was used to mimic the state of starvation and produce ketosis (Wilder, 1921). This led to the introduction of the so-called ''classical ketogenic diet,'' typically with a 4:1 ratio of fat (in grams) to protein and carbohydrate (in grams), for people with drug-resistant epilepsy. Later, in an attempt to make the diet more palatable, the medium chain triglyceride (''MCT'') KD was introduced on the premise that MCTs are more ketogenic per calorie, and the diet, therefore, allows a greater bulk of protein and carbohydrate (Huttenlocher et al., 1971; Huttenlocher, 1976). The MCT diet originally derived 60% of its calories from MCT oil. A modified MCT diet, designed to decrease gastrointestinal side effects, derives 30% of its calories from MCT oil and 30% from long-chain fats (Schwartz et al., 1989).

More relaxed variant forms of the diet have been proposed, including the Modified Atkins Diet (MAD) and the Low Glycemic Index Treatment (LGIT), aiming to provide increased flexibility and palatability. The MAD is based on a ratio of 1:1, although this is not necessary in all meals, and includes 10–30 g of carbohydrate/day (Kossoff & Dorward, 2008) with no restriction of fluids, calories, or protein. It allows users more flexibility and does not require the weighing of food portions or an initial hospital stay (Kossoff et al., 2009). The LGIT includes a higher proportion of carbohydrates (approximately 40–60 g/day) than the classical KD, with 60% of calories taken from fat, but only carbohydrates with a glycemic index of <50 relative to glucose are permitted.

A summary of the composition of these diets is found in Table 1. Fine-tuning by the dietician is customary.

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There is a relative dearth of data regarding the effectiveness of the KD compared to pharmacotherapy, but evidence for pediatric use of the KD is encouraging: a randomized controlled trial (RCT) with children and some adolescents has been conducted. Thirty-eight percent of participants (2–16 years) with at least daily seizures or more than seven seizures per week who had not responded to at least two antiepileptic drugs (AEDs), treated with a classical KD or MCT diet achieved >50% seizure reduction at 3-month follow-up, compared with 6% of controls; 7% of these treated individuals experienced a >90% seizure reduction compared with no controls (Neal et al., 2008). One-fourth of participants experienced side effects, such as vomiting, diarrhea, abdominal pain, constipation, hunger, and lack of energy during the 3 months of treatment. There were no significant difference in tolerability or the number of participants who achieved >50% or >90% reduction between the classical KD and MCT diet groups (Neal et al., 2009).

With such responder rates from dietary treatment in children, it is appropriate to evaluate effectiveness and acceptance of dietary treatments in adolescents and adults. In particular, with increasing evidence supporting the more liberal ketogenic regimens, adverse effects and perceived restrictiveness should be less of a deterrent for their administration in older people. Further advantages of dietary treatment must not be overlooked, such as rapid initiation of therapy and avoidance of additional drug interactions.

Methods

We reviewed the evidence regarding the effectiveness, tolerability, and compliance of the KD and its variants in adolescents (12–18 years) and adults (>18 years) with drug-resistant epilepsy. A systematic search was conducted of the English-, Spanish-, and French-language literature using PubMed and Google Scholar. The keywords ''ketogenic diet,'' ''modified Atkins diet,'' ''medium chain triglyceride diet,'' and ''low glycemic index treatment'' were used, cross-referenced with ''adults/adolescents'' and ''epilepsy.''

Results

Information was identified for 122 adults from open-label studies, plus four adults from case reports and case series, and 82 adolescents for which age-specific details on the efficacy of the KD were given; data were available for 56 adults and 10 adolescents, plus a case series of one adolescent and three adults on the MAD. The studies are of limited quality, with one RCT and limited efficacy data from class II evidence; with the exception of the RCT (Neal et al., 2008, 2009), all are open-label, observational studies. Three studies used an intent-to-treat (ITT) analysis, all on the MAD (Kossoff et al., 2008; Weber et al., 2009; Smith et al., 2011).

The classical ketogenic diet

Efficacy

Three studies have reported use of the KD exclusively in adults (Sirven et al., 1999; Mosek et al., 2009; Klein et al., 2010), in addition to two case reports (Kossoff et al., 2007; Bodenant et al., 2008) and one case series of two adults (Wusthoff et al., 2010); all suggest relative efficacy. Three studies assessed adolescents and adults (Barborka, 1930; Mady et al., 2003; Nei et al., 2003) and two further studies included adolescents in addition to children, giving age-specific efficacy data (Panico et al., 2000; Neal et al., 2009). All participants from one adult study (Sirven et al., 1999) are included in a later study (Nei et al., 2003) (Sperling & Nei, 2004), so we will not refer to data from the earlier study.

A summary of data specifically on individuals aged >12 years on the classical KD is given in Table 2. Data from seven studies show that, on average, 100 of 206 (49%) of adolescents and adults achieved ≥50% seizure reduction; of these 100 individuals, 13 (13%) became seizure-free. From these studies, it seems that when users are compliant, the KD can be effective in treating adolescents and adults with drug-resistant epilepsy. People with symptomatic generalized epilepsy may respond better to dietary treatment than those with partial or idiopathic generalized epilepsy (Nei et al., 2003), and people with multiple seizure types may respond better than those with one seizure type (Mady et al., 2003), although further evidence is needed.

In a study of the KD as monotherapy in adolescents and adults with epilepsy (predating concepts of drug-resistant or responsive), it was stated that ''older patients…are the least likely to be benefitted'' (Barborka, 1930). Recent studies found no correlation between efficacy and age (Coppola et al., 2002; Mady et al., 2003). A greater than 50% seizure

Table 1. Composition of the ketogenic diets and its variants

Diet	Ketogenic ratio	% carbohydrate	% protein	% fat (LCT)	% fat (MCT)
Classical KD	4:1	4	6	90	0
MCT diet	3:1	19	10	11	60
Modified MCT diet	3:1	19	10	41	30
MAD	1:1	~10	~25	65	0
LGIT	0.6:1	10	30	60	0

KD, Ketogenic diet; MCT, medium chain triglyceride; MAD, modified Atkins diet; LGIT, low glycemic index treatment; LCT, long chain triglyceride.

Table 2. Summary of studies involving adults and adolescents treated with the classical ketogenic diet

Authors (year)	Study type	Sample size aged >12 years (adolescents/adults)[a]	Age range (years)	Syndrome/seizure types	Syndrome/seizure types with better response than others?	Duration (months)	Ketogenic diet ratio	Number of adolescent responders at end point (%) (50–89% reduction/≥90% reduction/seizure free	Number of adult responders at end point (%) (50–89% reduction/≥90% reduction/seizure free	Number of participants with increase in seizure frequency (%)	% dropout before end of study	Adverse side effects
Barborka, 1930	Retrospective	100 (25/75)	16–51	N/A	No	1–46	4:1	12 (12%) unknown 3 (3%)	32 (32%) Unknown 9 (9%)	9 (9%)	N/A	Migraines, hunger, fatigue, amenorrhea, elevated cholesterol
Panico et al., 2000	Prospective	4 (3/1)	13–19	LGS, PS	LGS	3–36	3:1–4.5:1	0 (0%) 3 (100%) 0 (0%)	0 (0%) 1 (100%) 0 (0%)	0 (0%)	N/A	Unknown in this age group
Mady et al., 2003	Retrospective	45 (mostly adolescents but unknown how many were aged 19)	12–19	MST, LGS, CPS, GTC, AS, MS, SPS, ATS	MST	12	3:1–4.5:1	7 (16%) 6 (13%) 0 (0%)		2 (4%)	66	Hair thinning, hair loss, increased bruising or bleeding, weight loss, amenorrhea, delayed puberty, stunted growth
Nei et al., 2003 (including adults from Sirven et al., 1999)	Prospective	25 + one child (0/25)	11–51	SGE, IGE, PS	SGE	0.13–25.5	4:1	>50% reduction in 9 (73%) with SGE >50% reduction in 2 (66%) with IGE >50% reduction in 3 (27%) with PE		17% with SGE 33% with IGE 27% with PE[b]	88	Weight loss, elevated cholesterol, reduced free carnitine levels, slight reduction in selenium
Mosek et al., 2009	Prospective	9 (0/9)	23–36	FS, with or without SG	No	3	3:1	N/A	2 (22%) 0 (0%) 0 (0%)	0 (0%)	78	Hunger, diarrhoea, weight loss, elevated total and LDL cholesterol, elevated triglycerides and lactic dehydrogenase levels
Neal et al., 2009	Randomized trial	10 (10/0) but no data for one adolescent	12–16	SGE, SFE	No	3	3:1–4:1	5 (50%) 0 (0%) 0 (0%)	N/A	2 (20%)	10	Unknown in this age group
Klein et al., 2010	Prospective	12 (0/12)	24–65	PGE, LRE	No	4–26	3:1–4:1	N/A	5 (42%) 0 (0%) 1 (8%)	1 (8%)	25	Nausea, diarrhoea, constipation, vomiting, abdominal cramps, mild intermittent hunger, weight loss, increased cholesterol and serum lipids

AS, absence seizures; ATS, atonic seizures; CPS, complex partial seizures; FS, focal seizures; GTC, generalized tonic–clonic; IGE, idiopathic generalized epilepsy; LRE, localization-related epilepsy; LGS, Lennox-Gastaut syndrome; MS, myoclonic seizures; MST, multiple seizure types; PGE, primary generalized epilepsy; PS, partial seizures; SFE, symptomatic focal epilepsy; SG, secondary generalization; SGE, symptomatic generalized epilepsy; SPS, simple partial seizures.

[a]Adolescents defined as 12–18 years; adults as >18 years.

[b]Taken from Fig. 1, p. 106: Sperling & Nei, 2004.

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Table 3. Summary of studies involving adults and adolescents treated with the modified Atkins diet

Authors (year)	Study type	Sample size aged > 12 years (adolescents/adults)[a]	Age range (years)	Syndrome/ seizure types	Syndrome/ seizure types with better response than others?	End point (months)	Number of adolescent responders at end point (%) (50–89% reduction/≥ 90% reduction/ seizure free	Number of adult responders at end point (%) (50–89% reduction/ ≥90% reduction/ seizure free	Number of participants with increase in seizure frequency (%)	% dropout before end of study	Adverse side effects
Kang et al., 2007	Prospective	1 (1/0)	14.4	DS with ATS	No	7	0 (0%) 0 (0%) 0 (0%)	N/A	0 (0%)	N/A	Vomiting
Kossoff et al., 2008	Prospective	30 (0/30)	18–53	CPS, MST, AS	No	6	N/A	6 (20%) 3 (10%) with 76–99% reduction 1 (3%)	0 (0%)	53	Lethargy, weight loss, elevated total cholesterol, leg swelling
Carrette et al., 2008	Prospective	8 (0/8)	31–55	CPS, CPS with occasional SG, LGS	No	6	N/A	1 (13%) 0 (0%) 0 (0%)	1 (13%)	63	Vomiting, headache, nausea, diarrhoea, constipation, weakness, weight loss, elevated total and LDL cholesterol
Weber et al., 2009	Prospective	7 (7/0)	12–17	SFE, LGS, MAE, JME	No	3	2 (29%) 1 (14%) 0 (0%)	N/A	0 (0%)	0	Unknown in this age group
Kossoff et al., 2010	Prospective	2 (2/0)	13–18	SWS with CPS	No	6	1 (50%) 0 (0%) 0 (0%)	N/A	0 (0%)	0	Weight loss, high peak total cholesterol
Smith et al., 2011	Prospective	18 (0/18)	18–55	PS with SG, MS, CPS, SPS	No	12	N/A	3 (17%) 0 (0%) 0 (0%)	7 (39%)	22	Weight loss (desired), left arm jerks

AS, absence seizures; ATS, atonic seizures; CPS, complex partial seizures; DS, Doose syndrome; JME, juvenile myoclonic epilepsy; LGS, Lennox-Gastaut Syndrome; MAE, myoclonic astatic epilepsy; MS, myoclonic seizures; MST, multiple seizure types; PS, partial seizures; SFE, symptomatic focal epilepsy; SG, secondary generalization; SPS, simple partial seizures; SWS, Sturge-Weber syndrome.

[a]Adolescents defined as 12–18 years; adults as >18 years.

reduction may be ''less frequent'' in subjects older than 12 years than in younger age groups (Maydell et al., 2001); these differences were not significant.

All 12 adults who achieved seizure freedom also maintained ketosis, based on urinary acetoacetate tested daily (Barborka, 1930); of the 44 who found no benefit, 8 never achieved ketosis, although another 8 of 44 who ''definitely benefitted'' from treatment never achieved ketosis. This study, however, included only individuals who successfully maintained the diet, thereby introducing selection bias (Hartman & Vining, 2007). Contemporary studies report maintained ketosis in >82% of participants (Sirven et al., 1999; Mosek et al., 2009), although treatment duration was sometimes short—only 3 weeks for one participant (Mosek et al., 2009). Despite achieving ''persistent ketosis'' in hospital, two patients were unable to maintain this at home (Sirven et al., 1999). High ketone levels may not correlate with improved seizure control (Sirven et al., 1999; Mosek et al., 2009).

Planned treatment duration has ranged from 12 weeks (Mosek et al., 2009)—although only two individuals completed this protocol—to 8 months (Sirven et al., 1999). The longest recorded treatment duration in a prospective study was 36 months, elected by one adult (Panico et al., 2000). If treatment is effective, the response is seen quickly: In all people who achieved >75% seizure reduction, the full extent of the response was seen during the first month of treatment, and in four subjects with daily seizures, it was reached within 4 days of diet initiation (Klein et al., 2010). Only Klein et al. (2010) evaluated the antiepileptic effect after KD discontinuation in adults: Seizure improvement did not outlast treatment.

Tolerability

The most common adverse effects from the KD, as seen from Table 2, are gastrointestinal side effects, altered bowel habit, weight changes, and an unfavorable lipid profile. With the exception of increased serum cholesterol and triglyceride levels, most side effects are mild and readily managed, although hunger has caused users to discontinue dietary treatment (Mosek et al., 2009). Weight loss may act as an incentive for some overweight and obese individuals, who may achieve a normal body mass index (BMI) with treatment (Klein et al., 2010). Weight loss is greatest in those who desire weight reduction and accordingly reduce calorie intake (Sirven et al., 1999), although care must be taken with adolescents and unintentional weight loss, with consequential decreases in energy (Mady et al., 2003). Serum lipids return to baseline within 3 months of stopping the KD, based on relatively short treatment periods (Klein et al., 2010). The use of low-carbohydrate diets in adults for >90 days has no significant adverse effect on serum lipid, fasting serum glucose and fasting serum insulin levels, or blood pressure (Bravata et al., 2003). There are no data regarding the long-term use of dietary treatment on bone health in adolescents and adults.

Other beneficial effects of the KD have been reported. ''Mental conception,'' whatever this means, improved in treated individuals, as well as relative freedom from infections and colds (Barborka, 1930). Fifty-six percent found that treatment alleviated constipation. In one study, 15 of 45 (33%) adolescents reported increased ''alertness and energy'' and, importantly, only three of these participants reported difficulties with their peers (Mady et al., 2003). It was concluded that tolerability of the KD in adolescents did not differ from that in children, and personal motivation was high. Mean global quality of life score (QOLIE-31-P) rose nonsignificantly from baseline during treatment in another study (Klein et al., 2010). Reports concerning tolerability of the KD in older people are inconsistent.

Retention

Dropout rates may be discouraging (Table 2). There is a tendency for poor compliance in individuals older than 12 (Lightstone et al., 2001; Maydell et al., 2001; Coppola et al., 2002), compared to younger individuals. Side effects influenced the acceptability of the diet, but where treatment was effective, most people continued. The most common reason for stopping treatment was lack of efficacy (Mady et al., 2003). The proportion of users who discontinued treatment due to adverse effects was wide-ranging, from 0% (Klein et al., 2010) to 25% (Mosek et al., 2009). Variation was also seen in discontinuation due to restrictiveness of the diet, from 0% (Mosek et al., 2009) to 22% (Mady et al., 2003). Perceived lack of peer acceptance in adolescents should also be considered (Lightstone et al., 2001).

In one study, more than half of potentially eligible people refused to participate due to perceived restrictiveness and complexity of the diet (Mosek et al., 2009). Nevertheless, at least one patient has followed the diet for over 20 years (Kossoff et al., 2007).

The modified Atkins diet

Efficacy

Three open-label studies have reported use of the MAD exclusively in adults (Carrette et al., 2008; Kossoff et al., 2008; Smith et al., 2011). Three studies have reported on adolescents in mixed cohorts of children and adolescents (Kang et al., 2007; Weber et al., 2009; Kossoff et al., 2010), and one case series has included one adolescent and three adults (Kossoff et al., 2003); results are wide-ranging. A summary of studies that include data specifically on individuals aged >12 on the MAD is given in Table 3. Data from six studies show that, on average, 18 of 66 (27%) adolescents and adults achieved ≥50% seizure reduction; of these 66 individuals, 1 (6%) became seizure-free.

Treatment may be slightly more effective in those with higher initial seizure frequencies and in younger adults

(Kossoff et al., 2008). No specific data were provided for the adolescents included in some studies, but age at diet onset (range 3–16 years) did not affect the probability of >90% seizure reduction (Kossoff et al., 2006, 2011). When seizure reduction occurred with the MAD, the effect was seen rapidly—within a median of 2 weeks (Kossoff et al., 2008).

One study found that, after an average of 3 days (range 1–8), all adults had positive results for urinary ketones, both in the morning and evening (Carrette et al., 2008). There was an overall decreasing trend of urinary ketosis during the diet period, but the four participants who had more than four blood samples analyzed had elevated serum acetoacetate and β-hydroxybutyrate; in two of these, values were high over the entire study period. In another study, all 28 adults who remained on the diet for at least 1 week became ketotic, but only 2 of 15 (13%) had moderate-large urinary ketosis after 6 months (Kossoff et al., 2008). Ketone levels do not always correlate with improved efficacy in adults (Kossoff et al., 2008; Smith et al., 2011) or in mixed cohorts of children and adolescents (Kossoff et al., 2006, 2010, 2011).

Tolerability

Common side effects of the MAD are gastrointestinal complaints and unfavorable lipid profiles. Weight loss was more common in adults who initially requested to lose weight (Kossoff et al., 2008). BMI reduction and diet effectiveness may be correlated (Kossoff et al., 2008), but another study did not find this (Smith et al., 2011).

Beneficial effects have also been reported, such as ''improved concentration, well being and fitness,'' ''more erect posture,'' ''more fluent speech,'' and improved mood (Carrette et al., 2008). Tolerability of the MAD in adults and adolescents appears similar to that of the KD. Long-term side effects of the MAD are unexplored.

Retention

The principal reason for treatment discontinuation seems to be lack of effectiveness—''most patients were motivated to continue it as long as seizures were reduced'' (Kossoff et al., 2008). This may be expected due to its relative ease of administration, although the MAD ''is not an easy diet to maintain'' (Kossoff & Dorward, 2008). Despite this, one 17-year-old, who remained on the diet for 1 year, managed to go on holiday, go to cafes with her friends, and even tapered lamotrigine treatment without losing seizure control (Weber et al., 2009).

In one study, only 18 of 130 eligible patients consented to begin dietary treatment (Smith et al., 2011).

Three of eight (37.5%) (Carrette et al., 2008) and 14 of 30 (47%) (Kossoff et al., 2008) adults completed the 6-month study periods. Fourteen of 18 (78%) adults completed a 12-month study period (Smith et al., 2011). In one case, all 14 participants who finished the trial chose to continue the diet afterwards (Kossoff et al., 2008). All seven adolescents completed a 3-month study trial (Weber et al., 2009) and two of two adolescents completed a 6-month trial (Kossoff et al., 2010).

Discussion

Data on dietary treatment in adolescents and adults are limited. The findings must be interpreted with care.

Dietary treatment can be effective for adolescents and adults with drug-resistant epilepsy. Considering all reports, an average of 43% of adolescents and adults achieve ≥50% seizure reduction; of these 43%, 12% become seizure-free. A tendency has been reported of better response in younger people (Barborka, 1930; Kossoff et al., 2008, 2010). Only two studies, however, found a significant correlation between age and treatment effectiveness, in participants younger than 5 years of age compared to those aged 5–16 years (Wirrell et al., 2002), and in individuals younger than 12 years compared to those aged 12–29 years, but only at 6-month follow-up (Maydell et al., 2001). Most encountered no difficulties in initiating and maintaining ketosis in older people, but levels of ketones may not correlate with increased treatment effectiveness with the classical KD (Sirven et al., 1999; Mosek et al., 2009) or the MAD (Kossoff et al., 2006, 2008, 2010, 2011; Smith et al., 2011).

Syndrome or seizure type appears not to influence treatment outcome, although individuals with symptomatic generalized epilepsy (Nei et al., 2003) or multiple seizure types (Mady et al., 2003) may respond better to the classical KD.

Guidance on the duration of dietary treatment is limited, and only one study looked into the effect of the KD after its discontinuation, observing reduced benefit following cessation of treatment (Klein et al., 2010). This may represent a disparity between dietary treatment in children and older people, as the antiepileptic effect can persist in 80% of children at a median of 2.4 years (range 0–5.5 years) after stopping the diet (Martinez et al., 2007). Additional studies are warranted to determine optimal duration and whether the antiepileptic effects of the diet outlast treatment.

No direct comparison between adolescents or adults and children has been made of diet tolerability. From the limited data, no obvious serious adverse effects emerged in adolescents or adults. Two studies found that dietary treatment interfered with social interaction in adolescents (Lightstone et al., 2001; Mady et al., 2003), and none found that parental stress increased. Improved behavior, developmental progress, and alertness were also reported, and weight loss during treatment may provide further incentive for obese people.

Reports are inconsistent regarding retention in adolescents and adults compared to children. Despite limited sample sizes, retention appeared higher on the MAD than on the KD, and so more liberal regimens may be proposed as viable alternatives for older people. Percentage dropout with the KD ranged from 10–88% (mean = 53%) and from 0–63% (mean 28%) with the MAD (see Tables 2 and 3).

Many patients may also refuse to initiate dietary treatment in the first place.

Data on other KDs and variant forms including adolescents and adults are limited. One case report (Schiff & Lerman-Sagie, 1998), one open-label study (Trauner, 1985), and an RCT (Neal et al., 2008, 2009) included efficacy data specifically on individuals aged >12 on the MCT. Data are available for six adolescents: two had ≥50% reduction and one had increased seizures at 3-month follow-up (Neal et al., 2009); one achieved ≥50% seizure reduction at 6 months (Trauner, 1985). These effectiveness rates are similar to the KD and MAD, although larger sample sizes are needed for a more precise comparison.

The lower ketogenic ratio of the MCT diet might be predicted to improve tolerability due to greater freedom for carbohydrate intake, variety of food, more substantial portion sizes, and possible exchanges. In one study, however, all four adults found the high-fat diet unacceptable and large quantities of MCT oil unpalatable (Schwartz et al., 1989): ''[the diet] was more disruptive to their lifestyle than their seizures,''

One study included seven adolescents and one adult treated with the LGIT; three of seven (43%) adolescents and one of one (100%) adult achieved ≥50% seizure reduction (follow-up 1–12 months) (Coppola et al., 2011). Compliance was poor in this age group: four of seven (57%) adolescents remained on the diet for 2 months or less. No adverse effects were reported. Another study included people up to 22 years old treated with the LGIT, but no age-specific information is available (Muzykewicz et al., 2009). It is of interest to note that although changes in serum ketone levels from baseline were significant at 1-, 6-, and 9-month follow-ups, ketosis was not correlated with treatment effectiveness at any time point. Effectiveness of the LGIT appears similar to that of the KD and MAD but, despite no side effects, adherence to the diet may be difficult for adolescents and adults.

Dietary treatment can be effective (≥50% seizure reduction) for people with drug-resistant epilepsy, but tolerability is poor; alternative ways of achieving the same benefits are needed. This requires a better understanding of the mechanisms of seizure control in dietary treatments. There are many hypotheses regarding the antiepileptic mechanisms of the KD, which have been reviewed elsewhere (Rho & Sankar, 2008; Bough & Dingledine, 2009; Nylen et al., 2009), including indirect action from ketone bodies, enhanced brain energy reserves, increased mitochondrial biosynthesis, decreased glycolysis, enhanced γ-aminobutyric acid (GABA)ergic inhibition, decreased concentration of reactive oxygen species, increased leptin, and the action of polyunsaturated fatty acids on sodium, calcium, and potassium channels.

Several of these hypotheses invoke altered gene expression. One is the upregulated expression of the gene encoding the first enzyme of ketogenesis, mitochondrial 3-hydroxy-3-methylglutaryl-coenzyme A (CoA) synthase (Cullingford et al., 2002); another is reduced *BNDF* and *NTRK2* gene expression by increased 2-deoxy-D-glucose concentration and a consequent decrease in glycolysis, which reduces neuronal excitability (Huang & McNamara, 2006). Altered expression of genes involved in reactive oxygen species metabolism and oxidative stress (Stafford et al., 2010) and systemic activation of the genes in Nrf2 pathway (Milder et al., 2010) have also been proposed. Perhaps further study of these effects could bring us closer to providing individuals with the benefits of dietary treatment without the side-effects that impair compliance.

In conclusion, the KD and its variants may be effective for almost a half of adolescents and adults with drug-resistant epilepsy. However, studies are limited, including a small number of subjects, and only three studies used an ITT analysis. Side effects are usually transient and the most common reason for discontinuation of treatment is lack of effectiveness, but retention levels are poor compared to other treatment modalities. Trials of the more liberal dietary regimens in adolescents and adults, including whether there is a lasting antiepileptic effect of the diets, are warranted. Further study into the mechanisms underlying treatment effects of the KD might allow the same treatment effects to be achieved using novel, better-tolerated, nondietary approaches.

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