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Review

Cognitive benefits of the ketogenic diet in patients with epilepsy: A systematic overview

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ABSTRACT

The ketogenic diet (KD) has been found to be effective in reducing seizures in patients with treatment-refractory epilepsy. Less attention has been paid to additional cognitive benefits of KD. The aim of the present paper was to provide a comprehensive overview of the studies reporting effects on cognition after KD treatment in adults and children with epilepsy. To address this aim, the clinical literature on cognitive effects of KD in patients with epilepsy was reviewed using a systematic approach. We conclude that using subjective assessments of the patient's experience, cognitive improvements are frequently reported during KD treatment in the domains of alertness, attention, and global cognition. Studies that used objective neuropsychological tests confirmed benefits on alertness but found no improvement in global cognition. There are indications that these improvements are caused by both seizure reduction and direct effects of KD on cognition. The improvements appear to be unrelated to medication reduction, age when KD is started, type of KD, and sleep improvement. The findings in the present overview contribute to a better understanding of the beneficial effects of KD in patients with epilepsy.
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1. Introduction

1.1. Epilepsy

Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures. Cognitive deficits are often reported in patients with epilepsy [1–4]. The impairments in cognition are thought to be due to a complex interplay between seizures, brain damage, and treatment [5, 6]. The severity of cognitive problems depends on age at epilepsy onset, seizure type, medication use, and etiology. Patients with chronic, frequent seizures and high medication use are particularly affected by cognitive problems [5, 7].

In the majority of patients with epilepsy, seizures can be controlled by antiepileptic drugs (AEDs). Unfortunately, in 30% of the patients, these drugs are not efficacious, a condition called drug-resistant, intractable, or refractory epilepsy [8]. In addition, some patients experience severe undesirable side effects of the AEDs, leading to discontinuation of AED use [9–11]. In these cases, nonpharmacological treatments may be considered, such as the ketogenic diet (KD).

1.2. KD

Ketogenic diet is a high-fat, low-carbohydrate diet that induces ketosis. Ketosis is a metabolic state where the body uses ketone bodies, made from the breakdown of fatty acids in the liver, rather than carbohydrates as primary source of energy. The classical KD (cKD) has a fat to carbohydrate plus protein ratio of 3–4:1. Less restricted forms are available as well, such as the modified Atkins diet (MAD). In this diet, patients are encouraged to eat fat; however, there is no protein restriction [12]. Additionally, cKD and MAD can be supplemented with either long- or medium-chain triglycerides (LCT or MCT) to maintain the appropriate ratio and improve effectiveness [13–15]. The diets appear to be highly effective as 36–85% of the patients with epilepsy experience more than 50% seizure reduction when on KD [14, 16–19]. Multiple epileptic syndromes, such as glucose transporter 1 (GLUT1) deficiency, are especially responsive to KD [20].

1.3. Cognitive effects of KD in epilepsy

Most studies on KD focus on the impact of the diet on seizure control. Less attention has been paid to additional benefits of KD treatment, such as the effect on cognition. Cognitive improvement has

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Table 1
Overview of clinical studies reporting cognitive effects with KD treatment in patients with epilepsy.
cKD = classic ketogenic diet; MAD = modified Atkins diet; MCT = medium chain triglycerides; GLUT1 = GLUT1 deficiency syndrome; CSWS = continuous spike during slow wave sleep; MSNPE = myoclonic status in nonprogressive encephalopathy; TSC = tuberous sclerosis complex; PDC = pyruvate dehydrogenase complex deficiency.

Study	Cognitive domain								Diet	Number of patients	Age of patients	Epilepsy subtype	Diet duration	Seizure efficacy[a]	Cognitive assessment	Cognitive outcome
	Attention	Alertness	Adaptability	Concentration	Learning & memory	Language	Global cognition	Cognitive development								
	Parent reports															
Park et al., 2017 [23]							X		cKD or MAD	12	2.9-76.5	TSC	3-44 months	83.3%	Subjective: patient experience	75% improved, 8.3% worsened
Alqhatani and Mahmoud, 2016 [24]		X							cKD	30	0.5- 15 years	Mixed	Undefined	76%	Subjective: patient experience	60% improved
Maydell et al., 2001 [25]		X							cKD	143	0.5-29 years	Mixed	1 week – 58 months	30%	Subjective: patient experience	48% improved
Farasat et al., 2006 [21]							X		cKD	100	0.5-15 years	Mixed	6 months	70%	Subjective: patient experience	62% improved
Pulsifer et al., 2001 [26]	X								cKD	34	1.5-14 years	Mixed	12 months	79%	Subjective: Child behaviour checklist	Significant improvement in total group
								X							Subjective: Developmental profile 2nd edition	Significant improvement in total group
	Retrospective studies															
Thompson et al., 2017 [27]		X							cKD	4	6-10 weeks	Mixed	10 months – 2.5 year	75%	Subjective: parental experience	100%
Caraballo et al., 2017 [28]							X		cKD	6	2.5-9 years	MSNPE	1-3.5 years	80%	Objective: undefined tests	100%
Alter et al., 2015 [29]							X		cKD	12	0.1-31 years	GLUT1	8.9-23 years	100%	Objective: PPVT-III, Raven Coloured Matrices, Beery test	No significant improvements
Fujii et al., 2016 [30]								X	MAD/ cKD	12	3-35 years	GLUT1	1-96 months	79%	Objective: Kyoto Scale of Psychological Development	No significant improvements
							X								Objective: WISC-III and TBS	No significant improvements
Laux and Blackford, 2016 [31]		X							cKD	20	1-10 years	Dravet	6 months – 5.6 years	65%	Subjective: patient experience	75% improved
Eun et al., 2006 [32]								X	cKD	34	1-14 months	Infantile spasms	1-36 months	63%	Objective: Bayley developmental test	44% improved
Nordli et al., 2001 [33]		X							cKD	34	Mean 14 months	Mixed	Undefined	55%	Subjective: patient experience	Majority of patients improved
Vaisleib et al., 2004 [34]		X							cKD	54	0-18 years	Mixed	1-58 months	65%	Subjective: patient experience	37% improved
Kinsman et al., 1992 [35]		X							cKD	58	1-20 years	Mixed	1-48 months	67%	Subjective: patient experience	28% improved
Kossoff et al., 2004 [36]		X							cKD	81	0.5-15 years	Mixed	6 months	47% >90% improvement	Subjective: patient experience	58% improved
Leen et al., 2010 [37]		X							cKD	37	5-21 years	GLUT1	Undefined	86%	Subjective: patient experience	51% improved
Nabbout et al., 2011 [38]	X								cKD	15	4-11 years	Dravet	3-12 months	66%	Subjective: Conners and Achenbach scale	86% improved
	Prospective studies															
Carrette et al., 2008 [39]				X					MAD	3	3-4 years	Mixed	6 months	33%	Subjective: patient experience	100% improved
Gumus et al., 2015 [40]		X							cKD	4	2-11 years	GLUT1	Undefined	100%	Subjective: patient experience	100% improved
				X											Subjective: patient experience	100% improved
							X								Objective: WISC-IV and SBISC-IV	No significant improvements
Nikanorova et al., 2009 [41]	X								cKD	5	8-13 years	CSWS	9-36 months	40%	Subjective: patient experience	40% improved
							X								Objective: WISC-III	No significant improvements
Ramm-Pettersen		X							cKD/MAD	6	2-64	GLUT1	6-17	100%	Subjective: patient	100% improved

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