Chapter 3
Ketogenic Diet: Implications for Treatment and Injury in Neuropsychiatry and Motor Functioning

Fatima Dakroub, Habib Alkalamouni, and Rayan Dakroub

Contents

Habib Alkalamouni and Rayan Dakroub contributed equally to this work.

F. Dakroub (✉) · H. Alkalamouni
Department of Experimental Pathology, Immunology and Microbiology, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

R. Dakroub
Laboratory of Cancer Biology and Molecular Immunology, Faculty of Sciences, Lebanese University, Hadat, Lebanon

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Abstract The robust evidence of the ketogenic diet's (KD) success in the management of epilepsy has encouraged conducting studies on its effects in other neurological diseases. Despite disparities in characteristics, symptoms, and pathogenesis, these diseases share similar mechanisms that can be targeted by KD. The latter has been implicated in various neuroprotection processes, including neuronal energy replenishment, inflammation reduction, and gut microbiota modulation. Here, we review evidence from literature on the role of KD in the management and treatment of neuropsychiatric disorders and motor dysfunction. We provide an overview of preclinical and clinical assessments to identify the current gaps that need to be filled in future research studies. Finally, we summarize the various adverse events that may be associated with KD implementation.

Keywords Ketogenic diet · Neuropsychiatry · Motor dysfunction · Neuroprotection · Oxidative stress

Abbreviations

ACA	Acetoacetate
AD	Alzheimer's disease
AIS	Abbreviated Injury Score
ALS	Amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase
ASC	Apoptosis-associated speck-like protein containing a CARD
ASD	Autism spectrum disorder
ASIA	American Spinal Injury Association
BDH	β-Hydroxybutyrate dehydrogenase
BHB	Beta-hydroxybutyrate
BMC	Bone mineral contents
BMD	Bone mineral density
CARS	Childhood autism rating scale
CAU	Care as usual
CNS	Central nervous system
CPZ	Cuprizone
DA	Dopamine
DMD	Duchenne muscular dystrophy
EAE	Experimental autoimmune encephalomyelitis
EPM	Elevated plus maze
FST	Forced swim test
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HDL	high-density lipoprotein
HFD	High-fat diet
IBM	Inclusion body myositis

KB	Ketone bodies
KD	Ketogenic diet
KDTs	Ketogenic Dietary Therapies
KME	Ketone monoester
LDL	Low-density lipoprotein
LGIT	Low glycemic index treatment
LPS	Lipopolysaccharide
MAD	Modified Atkins diet
MCT	Medium-chain triglyceride diet,
MDD	Major depressive disorder
MeS	Metabolic syndrome
MS	Multiple sclerosis
OFT	Open field test
PAS	Parkinson Anxiety Scale
PCS	Post-concussion syndrome
PD	Parkinson's disease
RES	Reactive electrophile species
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
R-SDS	Repeated social defeat stress
SCI	Spinal cord injury
SD	Standard diet
TBI	Traumatic brain injury
UPDRS	Unified Parkinson's Disease Rating Scale
VHF-KD	Very-high-fat ketogenic diet
WD	Western diet

3.1 Introduction

There are two high-fat diet (HFD) types: the ketogenic diet (KD) and the Western diet (WD). The former is a low-carbohydrate and high-fat diet that aims to decrease the glucose dietary intake, inducing ketosis state. For many decades, the KD has been used for weight loss, metabolic disorders, and seizure management in pediatric patients (Kinsman et al. 1992). Four forms of ketogenic dietary therapies (KDTs) are available: the classic KD, the medium-chain triglyceride diet (MCT), the modified Atkins diet (MAD), and the low glycemic index treatment (LGIT) (Kapoor et al. 2021). A 3:1 to 4:1 fat-to-carbohydrate ratio is used in a classic KD. The MAD restricts carbohydrates to 20 g/day while increasing the fats. Unlike classic KD, it is possible to commence the MAD treatment on an outpatient basis. Medium-chain triglycerides are used as the ketogenic source in the MCT, thus facilitating the relative liberalization of carbohydrates. Finally, the LGIT employs complex carbohydrates that have a high glycemic index. The WD, on the other hand, is a high-

carbohydrate and high-fat diet directly associated with conditions like obesity and metabolic syndrome (MeS) (Kopp 2019). MeS is defined by the occurrence of at least three of the following morbidities: hypertension, hyperglycemia, hypertriglyceridemia, visceral obesity, and low high-density lipoprotein (HDL) levels (Grundy et al. 2005). Many preclinical studies that investigated the KD effect on neurodegenerative disorders provided evidence that it improves various outcome measures and reduces pathology (Brady et al. 2022; Brownlow et al. 2013; Liu et al. 2020; Yang and Cheng 2010). Moreover, clinical studies also suggested that KD ameliorated the quality of life in patients suffering from various neurological diseases (Phillips et al. 2018, 2020, 2021). This granted the topic of KD in neuroprotection a heightened attention within the scientific community. The "neuroketotherapeutics" term is now utilized to indicate the utilization of ketosis for the amelioration of neurological disorders. The safe and effective ketone blood concentration target range was reported to be between >0.2 and 5–8 mM (Hashim and VanItallie 2014). Notably, KD is still not recommended for tackling symptoms and decreasing the degeneration pace in neurological conditions, except for epilepsy. This chapter illustrates the various KD and HFD effects on neuropsychiatric conditions. Moreover, it summarizes their impact on the motor dysfunction associated with many neuromuscular diseases. Furthermore, it describes the mechanisms that may be implicated in the KD neuroprotection effects. Finally, it highlights the key knowledge gaps and research needs related to KD as a potential treatment in neuropsychiatry and motor dysfunction.

3.2 Ketone Body Metabolism

Ketone bodies (KB) play a role as alternative fuels for metabolism in the brain. This sustains ATP production, mitochondrial function, and survival of neurons. Ketogenesis is a process by which ketone bodies are produced. Beta-hydroxybutyrate (BHB), acetoacetate (ACA), and acetone are the most well-known KB. They are used as surrogate sources of metabolic energy when glucose stores become depleted in the body. The glycolytic inhibition in KD triggers ketogenesis, which occurs mainly in liver hepatocytes (Puchalska and Crawford 2017), neuronal cells, and epithelium of the retinal pigment (Adijanto et al. 2014). β-Oxidation reactions transform fatty acids originating from the diet into acetyl-CoA. The latter is further processed into ACA and BHB through the action of various cofactors and enzymes (Gough et al. 2021). Monocarboxylate transporters transport the obtained ketone bodies out of the liver into the blood. The brain and other organs take up the ketone bodies and reconvert them into acetyl-CoA through ketolysis. The integration of acetyl-CoA into the Krebs cycle produces GTP and ATP in the mitochondria. Moreover, β-hydroxybutyrate dehydrogenase (BDH) can convert back BHB into acetoacetate. This generates NADH, which in turn assists the function of the electron transport chain. Acetone is mainly excreted outside the body through exhalation. However,

the metabolism of acetone may yield lactate, acetate, and pyruvate. These products can serve as additional energy sources for the cells.

3.3 KD Neuroprotection Mechanisms

3.3.1 Energy Supplementation

Neurological diseases are often associated with changes in glucose metabolism. The main benefit from KD is its ability to restore the energy supply to neuronal cells. In the MPTP neurotoxicity murine model, BHB was shown to act on complex II resulting in the prevention of mitochondrial respiration decline and ATP production restoration (Tieu et al. 2003).

3.3.2 Reduction of Inflammation and Oxidative Stress

Neuroinflammation represents an innate reaction to neuronal damage and disease. To repair neuronal injury, phagocytosis is enhanced by inflammatory cells. Moreover, the secretion of neuroprotective and anti-inflammatory molecules is induced (Yong et al. 2019). However, the release of neurotoxic and inflammatory molecules and the reactive oxygen species (ROS) accumulation during unregulated neuroinflammation can exacerbate neuronal loss. KD can protect against neuroinflammation by inducing anti-inflammatory pathways. AMP-activated protein kinase (AMPK) is a protein that can sense energy levels in the cells. When the levels of energy are below average, AMPK is activated to decrease the consumption of ATP. Moreover, AMPK plays a role in regulating inflammation by activating NF-κB. The latter promotes the transcription of TNFα, IL-1β, and IL-6 (Nunes et al. 2015), which serve as pro-inflammatory molecules. KD was found to reduce AMPK activation in a glaucoma mouse model, leading to reduced expression of pro-inflammatory molecules (Harun-Or-Rashid and Inman 2018). In the central nervous system (CNS), the NLRP3 inflammasome represents a key mediator of inflammatory signaling. BHB inhibits NRLP3 inflammasome activation by blocking the ATP-induced ASC oligomerization and the potassium efflux required for inflammasome assembly (Youm et al. 2015). The mitochondrial dysfunction secondary to neuronal injury leads to the generation of ROS, reactive electrophile species (RES), and reactive nitrogen species (RNS). These molecules are associated with neuronal death and neurotoxicity in neuronal diseases (Espinós et al. 2020). A study demonstrated the role of BHB in scavenging ROS and hydroxyl radicals (Haces et al. 2008). Moreover, BHB preserved mitochondrial functioning and increased cell survival by directly reducing cellular ROS levels. Another study showed that KD decreased the expression of the oxidative stress marker malondialdehyde in a murine model of multiple sclerosis (MS) (Liu et al. 2020).

Moreover, KD induced the activity of glutathione peroxidase, an enzyme that decomposes H2O2. The KD impact on oxidative stress markers was associated with ameliorated improved myelination in the hippocampus.

3.3.3 Gut Microbiome Interaction

Various metabolites are secreted by microbial species in the gut. These include short-chain fatty acids, immunomodulatory molecules, neurotransmitters, and tryptophan. Indeed, several neurological disorders are associated with microbial derived molecules from the gut microbiome. CNS homeostasis and possibly neuroprotection may be affected by KD-induced alterations in the microbiome (Zhu et al. 2020). Olson et al. utilized two murine epilepsy models to demonstrate that mice fed KD had increased levels of the *Akkermansia* and *Parabacteroides* gut bacteria species (Olson et al. 2018) and significantly fewer seizures. KD led to a decrease in gamma-glutamyl transpeptidase in the stomach leading to increased production of GABA in the brain.

3.3.4 Epigenetic Regulation

The histones in the promoters of active genes can be modified directly on lysine residues by BHB (Xie et al. 2016). This process is known as β-hydroxybutyrylation, a major epigenetic regulatory pathway, with more than 1300 proteins identified as targets for ketone-related modifications (Huang et al. 2021). Thus, KD may influence epigenetic regulation through the upregulation of ketone bodies.

3.4 KD Effects on Neuropsychiatric Disorders

3.4.1 Anxiety and Depression

HDL is lowered in several neuropsychiatric diseases such as major depressive disorder (MDD) (Péterfalvi et al. 2019), bipolar disorder, and schizophrenia. Moreover, the degree of reduction in HDL is associated with the severity and duration of symptoms in MDD (Aksay et al. 2016; Lehto et al. 2010). Clinical studies show that KD increases HDL levels (Sharman et al. 2002) while decreasing those of the low-density lipoprotein (LDL) cholesterol (Dashti et al. 2004). Moreover, KD is strongly linked to an elevated ratio of GABA/glutamate (Calderón et al. 2017). This suggests a favorable effect of KD on the prognosis of neuropsychiatric diseases in which reduced GABA and/or HDL levels are involved. To explore the antidepressant effects of KD, a study used the Porsolt test, which is an in vivo depression

model (Murphy et al. 2004). The rats on KD displayed behavior similar to those on antidepressants. They spent less time immobile and had a lower chance of exhibiting "behavioral despair." KD coupled with regular voluntary exercise was shown to reduce depression and anxiety in Balb/c mice (Gumus et al. 2022). Additionally, these mice had increased levels of BHB and lower insulin and glucose levels. Moreover, their LDL/HDL ratio was reduced. Lower anxiety and depression levels were reflected by a decrease in the time spent in periphery walls of open field test (OFT) and in the closed arms of elevated plus maze (EPM) and reduced immobility time in the forced swim test (FST). Further research is required to improve our knowledge of the mechanisms by which the nervous system and behavior are influenced by pairing KD with voluntary exercise. KD treatment was found to dramatically ameliorate depressive-like behaviors in the lipopolysaccharide (LPS) and repeated social defeat stress (R-SDS) murine models of depression (Guan et al. 2020). The study further shows that KD reverses the neuronal excitability induced by LPS or R-SDS in the lateral habenula of mice. KD additionally rescues these mice from the vigorous activation of microglial cells in the lateral habenula. Another study showed that sociability is increased in CD-1 mice fed KD (Arqoub et al. 2020). Female and male CD-1 mice were subjected gestationally to KD or standard diet (SD) and cross-fostered at birth with dams fed SD. From that point onward, they remained fed with SD. At 10 weeks of age, they were tested for depressive-like behaviors with the forced swim test and for sociability with the three-chambered test. Additionally, their brain tissue was processed by immunohistochemistry to assess the expression levels of oxytocin in the hypothalamic and limbic areas. Although oxytocin expression was not affected in the quantified areas, the KD offspring had reduced depressive-like symptoms and increased sociability. Thus, gestational exposure to KD has a lasting positive impact on developmental disorders associated with behavioral disturbances in mice. A study by Sussman et al. demonstrated that depression behaviors were less likely in the offspring of mice fed KD during pregnancy (Sussman et al. 2015). In addition to reduced proneness to depression and anxiety, this offspring showed an elevated physical activity level both in utero and postnatally. In conclusion, published evidence from preclinical studies has further strengthened the notion of induced ketosis in psychiatry as "food for thought."

Campbell et al. explored the role of KD in mood stabilization in 274 people with bipolar disorder (Campbell and Campbell 2019). The majority of participants (85.5%) reported a favorable effect from KD on mood stabilization. Moreover, KD was found to be superior over other diets and significantly associated with higher odds of mood stabilization or diminution of symptoms. KD was also linked to reduced depression episodes, increased energy, weight loss, and improved speech coherence. A clinical assessment of 16 adults with Parkinson's disease (PD) on KD reported anxiety symptom alleviation evaluated using the Parkinson Anxiety Scale (PAS) (Tidman et al. 2022). A case report revealed the safety and effectiveness of KD in ameliorating health biomarkers, anxiety, and depression in a 68-year-old female patient suffering from stage I PD (Tidman 2022). Epilepsy is a common neurological disorder associated with wide-ranging neuropsychiatric manifestations.

A retrospective study conducted at the Johns Hopkins Adult Epilepsy Diet Center examined the psychiatric impact of MAD on chronic epilepsy (Shegelman et al. 2021). An association was reported between fewer symptoms of depression and anxiety and a longer diet duration in adults with epilepsy. However, significant changes in anxiety or depressive symptoms were not experienced in prospective participants on MAD in the same study. Still, a significant correlation between responder rate ($\geq$50% seizure reduction) and higher ketone level was found in the prospective cohort. Ijff et al. evaluated the KD impact on the cognitive function and behavior of adult epilepsy patients (IJff et al. 2016). In this randomized clinical trial, a total of 50 patients were included. Compared to the group that received care as usual (CAU), the KD group was appraised as being more productive and exhibited reduced anxious behavior and mood disturbances.

3.4.2 Addiction

Somatic and mental health can be adversely affected by alcohol abuse (Probst et al. 2014). Indeed, alcohol dependence is associated with the development of psychiatric disorders such as depression (Kessler et al. 1997). A recent study by Blanco-Gandía et al. found that mice on KD had a net reduction in alcohol consumption compared to the SD group (Blanco-Gandía et al. 2021). However, their motivation to drinking remained the same. Moreover, KD was found to decrease the severity of alcohol withdrawal symptoms in a clinical cohort of 19 inpatients with alcohol-abuse disorder (Wiers et al. 2021). The KD treatment was administered for 3 weeks and resulted in reduced dependence on psychoactive drugs during detoxification.

Studies also showed that KD had effects on drug addiction. It was shown that OF1 male mice fed KD needed lower numbers of sessions to eliminate drug-related memories. In addition, KD inhibited the reinstatement of drug seeking triggered by cocaine priming. However, KD did not prevent the mice from acquiring drug-conditioned place preference (Ródenas-González et al. 2022). Another study suggested that KD acts on drug addiction by directly influencing dopamine-linked behaviors (Martinez et al. 2019). The authors demonstrated that mice fed KD followed by cocaine treatment showed a reduction in cocaine-induced behaviors in comparison to the control group. Hence, KD possesses a therapeutic potential for cocaine addiction and possibly other drugs.

KD was described recently as a potential treatment for eating disorders. A recent pilot clinical study reported weight loss and improvement of binge eating and food addiction symptoms in five women (Rostanzo et al. 2021). The authors concluded the feasibility and potential of KD in the treatment of high-calorie food addiction. A case series revealed that KD was feasible and well tolerated in three patients with excessive eating disorders (Carmen et al. 2020). Both cravings and control-lack symptoms of food addiction were significantly decreased by KD. Moreover, fewer episodes of binge eating were obtained with KD treatment.

3.4.3 *Other Psychiatric Diseases*

KD may serve as a tool for the management and treatment of several psychiatric diseases. A case series of two females suffering from type II bipolar disease revealed the safety of management by KD and the lack of adverse events (Phelps et al. 2013). Moreover, the diet exerted beneficial effects such as mood stabilization and symptom improvement as reported by the patients. A case report implemented KD in the treatment of an elderly woman who had been suffering from schizophrenia since teenage years (Kraft and Westman 2009). KD successfully eliminated the psychotic symptoms, which the patient had been suffering for a long time. She stopped experiencing hallucinations that prompted suicidal thoughts and lost weight. Recent preclinical and clinical studies demonstrated that KD improves behaviors linked with autism spectrum disorder (ASD) in mice (Ruskin et al. 2017) and children (Lee et al. 2018). The KD benefits extend to various psychiatric disorders and deserve additional investigations in large clinical cohorts to assess both KD safety and efficacy.

3.5 Evidence for KD Effects in Diseases Associated with Motor Dysfunction

3.5.1 *Findings from Preclinical Studies*

Several studies assessed the KD effects in diseases associated with motor dysfunction. In vivo models of Alzheimer's disease (AD) (Beckett et al. 2013; Brownlow et al. 2013) and Parkinson's diseases (Shaafi et al. 2016; Yang and Cheng 2010) showed that KD improves motor function. In a rat model, Kuter et al. showed that long-term hyperketonemia from KD did not protect against the dopaminergic neuronal damage instigated by 6-OHDA (Kuter et al. 2021). However, KD improved the movement and motion of rats and normalized their dopamine (DA) turnover in the striatum. KD may not necessarily act against the neurodegeneration feature of PD. However, it may aid in bolstering the late compensatory mechanisms. Long-term and durable metabolic studies using standardized diet parameters are needed to evaluate the extent of the KD impact on PD. Multiple sclerosis is an autoimmune chronic disease in which the CNS is affected. It is marked by inflammation associated with the impairment of nerve cell processes and myelin. KD was demonstrated to have a neuroprotective effect in the hippocampus of the cuprizone (CPZ)-induced demyelination murine model (Liu et al. 2020). KD additionally reduced the lesion size and improved motor ability in CPZ mice. KD-treated mice had better motor coordination and remained significantly longer on the rotarod device. Another study utilized a murine model of autoimmune encephalomyelitis (EAE) to assess the KD effect on CNS inflammation (Kim et al. 2012). Both motor disability and CA1 hippocampal synaptic plasticity were improved by KD. In addition, the Morris

water maze assessment revealed better spatial learning and enhanced memory in the KD group. The authors concluded that KD attenuates the oxidative stress and robust immune response seen in EAE animals.

Repetitive motor behaviors are repetitious and monotonous movements with no recognized function. They are associated with different psychiatric and neurological diseases such as ASD. KD was applied in a rodent model to assess its effect on abnormal repetitive circling behavior (Brady et al. 2022). After older (15+ months) male and female mice were fed KD, less rounds of repetitive behavior were detected. The positive KD impact on repetitive motor behavior was replicated in female mice between 4 and 6 months of age. Moreover, pharmacological assessment suggested an increased expression of the D2 receptor in the indirect basal ganglia pathway. Thus, it is relevant to directly examine the KD effects on the dopamine receptor function. Duchenne muscular dystrophy (DMD) is a disease of genetic origin that is characterized by muscle weakness and atrophy. A KD that was supplied with medium-chain triglycerides was shown to significantly inhibit the key features of DMD in a rat model (Fujikura et al. 2021). This diet prevented muscle necrosis, inflammation, and subsequent fibrosis. Moreover, it increased muscle strength and fiber diameter and promoted the proliferation of smooth muscle cells. KD supported with medium-chain triglycerides ameliorates muscular dystrophy by enhancing muscle regeneration and inhibiting myonecrosis.

Diet and metabolic health go hand in hand. Many neurodegenerative and neuromuscular diseases are linked to mitochondrial dysfunction. Ahola-Erkkilä et al. demonstrated that KD delayed mitochondrial myopathy progression in transgenic deletor mice (Ahola-Erkkilä et al. 2010). These mice exhibited reduced levels of cytochrome c oxidase-negative muscle fibers. Moreover, KD completely halted the development of mitochondrial ultrastructural malformations in muscle cells. Additionally, KD restored the metabolic and lipidomic changes associated with mitochondrial myopathy to wild-type levels. Amyotrophic lateral sclerosis (ALS) is a chronic progressive neurodegenerative disease that does not have a known treatment. The loss of muscle control is one of the main features of ALS. KD was shown to alter the clinical and biological manifestations of ALS in a mouse model (Zhao et al. 2006). Baseline motor performance loss was delayed in mice that were fed KD. Moreover, motor neurons were more abundant in the spinal cord sections of KD-fed animals. The authors also demonstrated that BDH—a principal ketone body—protects motor neurons from cell death. Zhao et al. treated ALS mice with caprylic triglyceride, which is a medium-chain triglyceride that is metabolically transformed into ketone bodies (Zhao et al. 2012). The treatment group had significantly improved motor performance and were protected from spinal cord motor neuron loss. The authors suggested that caprylic triglyceride alleviated motor impairment in ALS rats through the restoration of energy metabolism.

Streijger et al. assessed the KD efficacy in the treatment of spinal cord injury (SCI) in a rat model (Streijger et al. 2013). The authors observed a stable improvement in the forelimb function of KD-fed rats compared to rats on a standard diet based on carbohydrates. Moreover, rats fed KD had more grey matter sparing and smaller lesions in their spinal cords. The ad libitum administration of KD in rats

post-SCI was shown to rescue mitochondrial function (Seira et al. 2021). KD improved post-SCI metabolism by altering the regulation of mitochondrial related genes, activating the NRF2-dependent antioxidant pathway, and increasing parameters of mitochondrial biogenesis. Zeng et al. further explored the KD mechanism of action post-SCI in Sprague-Dawley rats (Zeng et al. 2021). The transcriptome level changes and myelin expression were assessed in rats fed KD or standard diet (SD). The authors found that KD had reprogrammed the steroid metabolism in SCI treatment. Moreover, these alterations in the metabolism of steroids were introduced at the transcriptional level. Myelin areas were observed to be significantly vaster in SCI rats that were fed KD. Additionally, these rats had a significant decrease in the expression of genes implicated in immunological pathways. Thus, the KD-induced reprogramming of steroid metabolism may improve the myelin growth and immune microenvironment in rats with SCI. Traumatic brain injury (TBI) is a dysfunction in the brain resulting from an external force's impact on it. Har-Even et al. examined the cognitive, cellular, and molecular effects of KD post-injury using a closed-head murine model of TBI (Har-Even et al. 2021). The authors showed that KD reduces reactive astrocytes, mitigates TBI-induced neuroinflammation, and prevents TBI-induced neuronal loss. KD may represent a useful tool to bolster the protective mechanisms from injury in the brain. It may also constitute a prospective novel treatment for TBI. Mayr et al. called for the careful exploration of dietary effects on neurotrauma in animal models (Mayr et al. 2020). The authors demonstrated that KD did not play a role in the sensorimotor recovery in a mouse model of SCI. The sensorimotor behavior of the mice was examined post-injury using the von Frey, open field, and ladder-rung crossing tests. The authors concluded the need to assess ketogenic diets according to the category and position of neurotrauma. Moreover, it is essential to gather knowledge on the secondary injury mechanisms and the metabolic deficits' extent post-TBI or SCI.

3.5.2 Evidence from Clinical Evaluations

Several clinical studies exist on the effects of KD on the motor function and quality of life in patients with various neurological diseases. We summarized in Table 3.1 the clinical trials and case reports that evaluated KDTs in disorders associated with motor dysfunction. The KD efficacy and safety in AD seem promising, but additional randomized trials are needed. In a randomized clinical trial including 26 AD patients on KD, high rates of safety, adherence, and retention were obtained (Phillips et al. 2021). Patients on KD experienced an improvement in quality of life compared to patients following a usual low-fat diet with healthy eating guideline. Moreover, patients on KD had an ameliorated daily function. Results from the Ketogenic Diet Retention and Feasibility Trial revealed an improvement in cognitive function in AD patients on MCT-KD (Taylor et al. 2018). Most of the adverse events experienced in this study were related to MCT. The pilot study concluded by justifying additional KD trials in mild AD. A case report of an AD patient revealed beneficial effects from

Table 3.1 The clinical trials and case reports that evaluated KDTs in disorders associated with motor dysfunction

Condition	Type	Year	Number of patients	Intervention	Main findings	Reference
Parkinson's disease	Pilot study	2005	5	Hyperketogenic diet	KD improved the UPDRS scores including motor function	Vanitallie et al. (2005)
Acute spinal cord injury	Pilot clinical trial	2014	10	KD	KD is a safe and feasible treatment for acute SCI KD increased the average motor American Spinal Injury Association score	Guo et al. (2014)
Alzheimer's disease	Case report	2015	One 63-year-old male	Ketone monoester (KME)	KME is safe and well tolerated KME improved cognitive and daily activity performances	Newport et al. (2015)
Mitochondrial myopathy	Pilot study	2016	5	Modified Atkins diet (MAD)	All patients experienced adverse events (muscle damage)	Ahola et al. (2016)
Acute spinal cord injury	Pilot feasibility and safety trial	2018	7	KD	KD is a safe and feasible treatment for acute SCI KD significantly increased the extremity motor scores	Yarar-Fisher et al. (2018)
Alzheimer's disease	Pilot clinical trial	2018	10	MCT-KD	KD improves cognitive function	Taylor et al. (2018)
Parkinson's disease	RCT	2018	38	KD	KD is a safe and feasible treatment for Parkinson's	Phillips et al. (2018)

(continued)

Table 3.1 (continued)

Condition	Type	Year	Number of patients	Intervention	Main findings	Reference
					disease KD significantly improved motor and nonmotor symptoms	
Parkinson's disease	Pilot clinical trial	2019	14	KD	KD did not affect motor function in PD KD improved cognitive function in PD	Krikorian et al. (2019)
Sporadic inclusion body myositis (IBM)	Case report	2020	One 52-year-old female	KD	KD reduced muscle inflammation KD decreased the muscle atrophy rate The patient regained independent walking	Phillips et al. (2020)
Post-concussion syndrome (PCS)	Pilot feasibility study	2020	14	Very-high-fat ketogenic diet	KD is safe and feasible in PCS KD improves cognitive function	Rippee et al. (2020)
Alzheimer's disease	RCT	2021	26	KD	KD is a safe and feasible treatment for AD KD ameliorates the daily function in AD	Phillips et al. (2021)
Traumatic brain injury	Open-label, single-arm clinical trial	2022	10	KD	KD is a safe and feasible treatment for TBI	Arora et al. (2022)

(continued)

Table 3.1 (continued)

Condition	Type	Year	Number of patients	Intervention	Main findings	Reference

Abbreviations: *AD* Alzheimer's disease; *IBM* inclusion body myositis; *KD* ketogenic diet; *KME* ketone monoester; *MAD* modified Atkins diet; *PCS* post-concussion syndrome; *PD* Parkinson's disease; *QoL* quality of life; *RCT* randomized controlled trial; *SCI* spinal cord injury; *TBI* traumatic brain injury; *UPDRS* Unified Parkinson's Disease Rating Scale

ketone monoester (KME)—a potent ketogenic agent—administration (Newport et al. 2015). Throughout the 20-month treatment period, the patient tolerated KME well. Moreover, he ameliorated in cognitive performance, self-care, and daily activity. Phillips et al. compared KD to a low-fat diet in a total of 38 patients with PD (Phillips et al. 2018). Significantly improved nonmotor and motor symptoms were observed in both diet groups. The KD group had greater improvements compared to the group following the low-fat diet, but in nonmotor symptoms only. A controlled pilot trial revealed that motor function was not affected by KD in PD patients (Krikorian et al. 2019). However, cognitive performance was improved due to nutritional ketosis.

A case series evaluated the impact of KD in five PD patients who followed the diet for a duration of 28 days (Vanitallie et al. 2005). The authors observed improved Unified Parkinson's Disease Rating Scale (UPDRS) scores in all participants. The improvement included motor function, but the authors could not rule out the placebo effect. Additionally, cholesterol increases were prevented in four out of five patients due to the substitution of unsaturated fats with saturated ones. HFD is associated with a lower risk of ALS development (Fitzgerald et al. 2014; Veldink et al. 2007). However, the KD effect on motor function in ALS patients requires further clinical investigation. Sporadic inclusion body myositis (IBM) is an inflammatory disorder characterized by muscular degeneration and currently lacks a known treatment. In a case report of a female with deteriorating IBM, KD was chosen as the primary approach for treatment (Phillips et al. 2020). The patient on KD had substantial clinical improvement, with stabilization of muscle inflammation and reduction in the rate of muscle atrophy. The patient regained independent walking 1 year posttreatment.

In a case series by Ahola et al., five mitochondrial myopathy patients were managed with MAD (Ahola et al. 2016). However, all patients experienced major adverse events between 1.5 and 2 weeks posttreatment. Serious symptoms such as progressive muscle pain and drainage of muscle enzymes prompted the early cessation of the diet in all patients. The authors warned about the muscle damage effect that can be induced by MAD in a certain subgroup of the population. They concluded that disease progression can be modified by nutrition in mitochondrial disorders. They recommended the incorporation of dietary counseling in mitochondrial myopathy care.

In a pilot feasibility and safety trial, KD was found to be safe as a treatment for acute SCI (Yarar-Fisher et al. 2018). The study included seven patients with acute

SCI assigned to KD and standard diet groups. An improvement in the levels of inflammatory markers was observed in the sera of patients on KD. Compared to the SD group, KD resulted in significantly higher extremity motor scores. The safety and feasibility of KD were also demonstrated in a clinical trial that included ten acute SCI patients (Guo et al. 2014). During KD, glycemia remained in the normal range. Moreover, the liver and kidney function remained unchanged after KD. An increase in the average motor American Spinal Injury Association (ASIA) score was observed after KD. Another study evaluated the efficacy and feasibility of the very-high-fat ketogenic diet (VHF-KD) in patients with post-concussion syndrome (PCS) symptoms (Rippee et al. 2020). A total of 11 out of 14 participants achieved ketosis by implementing the VHF-KD (79% compliance). This confirmed the ability of PCS patients to achieve adherence to VHF-KD. Moreover, an improvement in cognitive function was observed, but the results need to be interpreted with caution. The study had limitations in its design including a small sample size and a single-arm nature. Arora et al. demonstrated the feasibility of adopting KD for the treatment of TBI (Arora et al. 2022). The study included ten male patients with TBI and an Abbreviated Injury Score (AIS)-Head $\geq$3. None of the participants experienced clinical adverse effects from KD. The authors justified the need for additional randomized controlled trials to decipher the KD dose, duration, and effects on TBI outcomes.

3.6 Adverse Effects of the Ketogenic Diet

The metabolic changes induced by KD force every cell to rely primarily on beta-oxidation for energy production (Yudkoff et al. 2008). This can lead to alterations in genetic regulation, hormonal pathways, and neurotransmitter production. Unless properly supplemented, people on KD are expected to have deficiencies in several essential vitamins, electrolytes, and trace minerals (Zupec-Kania and Zupanc 2008). A major challenge for KD implementation is achieving a good adherence level to dietary recommendations. Insufficient adherence may result in poor tolerance and a range of frequently encountered short-term side effects. The latter are known as keto flu and include symptoms such as nausea, vomiting, headache, fatigue, dizziness, insomnia, difficulty in exercise tolerance, and constipation (Masood et al. 2022). Adequate fluid and electrolyte intake can ameliorate some of these symptoms. Long-term side effects that usually present 3 months post-KD include kidney stones, fatty liver disease, hypoproteinemia, hyperlipidemia, reduced bone mass density, and vitamin and mineral deficiencies.

3.6.1 Hyperlipidemia

The incidence of hyperlipidemia is elevated in patients treated with KD (Nizamuddin et al. 2008). However, genetics and heredity play a significant role in its development (García-Giustiniani and Stein 2016). The majority of food allowed in KD contains a high amount of saturated fat, which can lead to an undesirable lipid profile. This is characterized by elevated levels of VLDL and LDL and a low level of the anti-atherogenic HDL (Fenton et al. 2009). By introducing minor modifications such as using oil instead of butter and substituting egg whites for whole eggs, a normal lipid profile can be restored. KD was also found to increase the levels of polyunsaturated fatty acids in the serum (Fraser et al. 2003). Fortunately, omega-3 supplementation seems to reverse this side effect, thereby reducing the risk of cardiovascular problems (Dahlin et al. 2007).

3.6.2 Cardiac Disease

A systematic investigation of the long-term KD effects on cardiovascular health is still unavailable. One case series reported two mortalities related to cardiac complications in children treated with KD (Bank et al. 2008). Both cases suffered from selenium deficiency that was associated with QC interval prolongation and cardiac dysfunction. Xu et al. showed that the upregulation of BHB—an HDAC2 inhibitor—induced the expression of high Sirt7 levels (Xu et al. 2021). This resulted in the inhibition of mitochondrial biogenesis and the subsequent cardiomyocyte apoptosis and cardiac fibrosis.

3.6.3 Linear Growth Failure

The restrictive KD nature in terms of calories and protein intake is known to cause a growth reduction in children (Bergqvist et al. 2008; Neal et al. 2008). The growth rate during preadolescent years is mainly driven by insulin-like growth factor-1 (IGF-1) and growth hormone (Laron 2001). Spulber et al. reported a dramatic decrease of IGF-1 in children on KD compared to baseline measurements (Spulber et al. 2009). Another study found that KD did not induce significant changes in growth hormone levels. However, KD triggered hepatic growth hormone resistance via the downregulation of growth hormone receptor expression (Bielohuby et al. 2011).

3.6.4 Gastrointestinal Disorders

Gastrointestinal (GI) complications can occur in up to 75% of cases on KD due to the lack of the fibers needed for normal GI function (Bergqvist 2012). Ketosis promotes the downregulation of acyl ghrelin, which may lead to anorexia and refusal to eat (Vestergaard et al. 2021). Moreover, clinical studies reported acute pancreatitis (Stewart et al. 2001) and gallstone disease (Hassan et al. 1999) in patients on KD. Still, KD may improve the outcomes of certain GI disorders such as gastro-esophageal reflux disease (GERD). A comparative study by Austin et al. revealed that a diet very low in carbohydrates ameliorated the symptoms of GERD in eight patients (Austin et al. 2006). Jung et al. suggested that abnormal endoscopy results before KD initiation may explain the frequency of GI symptoms posttreatment (Jung et al. 2008). They concluded the importance of supplementation with GI medications in improving the tolerance to KD.

3.6.5 Kidney Stones

Due to the metabolic changes associated with the KD, patients may develop kidney stones (Kielb et al. 2000). Urolithiasis, elevated levels of uric acid, and a lower urine PH were observed in pediatric patients treated with KD (Furth et al. 2000). This may be attributed to the high amount of acidic ketone bodies, hypercalciuria, and low urine citrate. Routine monitoring and frequent hydration can minimize the risk of developing kidney stones.

3.6.6 Compromised Bone Density

In adults, the evidence of negative changes in bone mineral density (BMD) and bone mineral contents (BMC) is scarce (Andersen et al. 1997). The changes in BDM seem to be more dramatic during the preadolescent phase rather than adulthood (Bonjour et al. 1991). Bone mineralization peaks around the end adolescence. Consequently, the BMD level accrual during this phase will directly influence the risk of osteoporosis and fractures during adulthood. Indeed, high level of ketosis had a negative correlation with growth rate and bone mass accumulation (Merlotti et al. 2021). It is also worth mentioning that antiepileptic drugs can predispose to osteoporosis depending on the length of treatment. These drugs may interfere with the vitamin D function and calcium deposition and directly affect bone remodeling (Fitzpatrick 2004).

3.7 Future Research Directions

The preclinical research conducted so far provides evidence on the beneficial KD impact and its mechanism of action in neuropsychiatric diseases and motor dysfunction. However, more studies are needed to discern the specific pathways involved in these mechanisms. The existing clinical studies and case reports on the role of KDTs in neurological diseases share many limitations. As a starter, there are no unified KD parameters that allow the accurate comparison of these studies. Hence, assessing the different KDTs and their components (e.g., ratios, doses, duration) can be a starting point for standardizing randomized clinical trials (Habashy et al. 2022). Moreover, the design of many existing studies suffers from the lack of randomization, being single arm and/or having a small sample size. Therefore, the current focus for future studies should be to conduct adequately planned clinical trials with solid protocols that ensure the generation of reliable results.

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