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Therapeutic effects of ketogenic diets on physiological and mental health

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Abstract

Ketogenic diets are emerging dietary patterns that have demonstrated potential as therapeutic tools in a variety of symptoms and conditions, such as epileptic seizures, diabetes, obesity, cancer, migraines, and metabolic syndrome. This narrative review examines the therapeutic effects of ketogenic diets on physiological and mental health, including their role in modulating the gut microbiome. Ketogenic diets promote weight loss, enhance insulin sensitivity, and may lower dyslipidemia, which are crucial factors in preventing cardio-metabolic diseases. They also play a significant role in the composition and function of the gut microbiome, serving as a therapeutic approach to control autoimmune diseases, given their effectiveness in reducing pro-inflammatory cells. Conversely, a potential downside of these diets is the decrease in beneficial bacteria that have been positively associated with human health. Regarding mental health, ketogenic diets have the capability to stabilize neural networks, improve neuroplasticity, and exert direct benefits in brain bioenergetics, thereby potentially alleviating the symptoms related to several mental conditions, such as epilepsy, anxiety, depression, schizophrenia, bipolar disorder, autism spectrum disorder, and certain neurodegenerative diseases. However, more randomized, long-term studies are required to assess their efficacy, sustainability, and safety, including methodological rigor to strengthen findings on dietary impacts.

Keywords

Ketogenic diets, physiological disorders, mental disorders, gut microbiome, therapeutic tool

Introduction

Nutritional psychiatry is a new area that links dietary habits to mental health and microbial function [1, 2]. Therefore, nutritional psychiatry must include the role of the gut microbiome as a diagnostic tool to identify targets for personalized treatments, and for integrative strategies that combine dietary, pharmacological, and psychological interventions.

Dietary patterns refer to the quantity, diversity, and types of foods and nutrients in a diet, as well as to the frequency of their consumption. Some of the major dietary patterns include: high-calorie diets such as the Western diet; mixed-balance diets such as the Mediterranean and Japanese diets; plant-based diets such as the vegetarian and vegan diets; and low-carbohydrate diets such as the ketogenic diet (KD). These diets exert diverse effects on physiological well-being, and share common attributes and characteristics [3–8]. However, adherence to a specific dietary pattern is influenced by geographic location, cultural norms, ethical beliefs, and environmental consciousness, as well as by physical health and psychological well-being [9–11].

The KD is an emerging dietary pattern, which consists of a normocaloric, high-fat, very low-carbohydrate diet that provokes a state of ketosis [12]. There are numerous reports in the literature stating that KD has a significant positive effect on epileptic seizures and mood disorders, thus suggesting KD as a potential therapeutic tool [13]. In addition, several modified KDs are currently widely applied to the treatment of obesity [14], diabetes [15], cancer [16], migraine [17], and metabolic syndrome [18]. However, the involvement of this diet in mental health outcomes, as well as its role in the modulation of the gut microbiome, has been poorly studied. For this reason, the present narrative review examines the therapeutic effects of the KD and its variants on physiological and mental health, including their role in modulating the gut microbiome.

Effects of KDs on physiological health

KDs have become increasingly popular due to their effects in promoting weight loss, enhancing insulin sensitivity, and potentially lowering dyslipidemia [14, 15, 19]. These factors are crucial in the prevention of cardio-metabolic diseases, which represent one of the most significant health challenges today [19], although there is no clear evidence regarding the advantageous effects of these diets on other cardio-metabolic risk markers [20].

There are diverse variants of KDs that primarily differ in their composition of fats, proteins, and carbohydrates. (i) The modified Atkins diet (MAD) consists of 65% fats, 25% proteins, and 10% carbohydrates [21]. In the classic KD, the ratio of fats and carbohydrates is 4:1. This ratio can be altered to 3:1 for moderating metabolism activity, with restricted calories and fluids. In contrast, the MAD does not require calorie, protein, or fluid restriction and may be a good alternative for patients who cannot tolerate a more restrictive diet like the classic KD [22]. (ii) The medium-chain triglyceride diet (MCTD) contains a higher production of ketone bodies (KBs) than any other types of fats, including long-chain triglycerides (LCT). This diet, which consists of 71% fats, 10% proteins, and 19% carbohydrates, is more appropriate for children because it diminishes the need for other micronutrients, and contributes to a lower cholesterol ratio, thereby decreasing the risk of cardiovascular disease [23]. (iii) Low glycemic index therapy (LGIT) is an alternative diet treatment consisting of 60% fats, 30% proteins, and 10% carbohydrates with a low glycemic index [24]. While the KD and MAD are associated with ketosis, the exact role of KBs in LGIT is unclear. For instance, Muzykewicz et al. [25] reported that of the 12 patients with less than 90% seizure reduction, only 33.3% had elevated serum levels of β-hydroxybutyrate (BHB) (0.7–1.7 mM). Therefore, it seems that ketosis is not required for optimal seizure control.

All KDs result in increased amounts of KBs, such as acetoacetate, BHB, medium-chain triglyceride (MCT), and acetone in the blood and urine [26]. These compounds are involved in several physiological mechanisms, including enhanced mitochondrial activity, inhibition of apoptotic proteins, reduction of oxidative stress, expression of antioxidant proteins, as well as modulation of autophagy, neurotransmitter levels [γ-aminobutyric acid (GABA), glutamate, and monoamines], and neuroinflammatory pathways [27–33]. In addition, KBs can act as an alternative energy source when glucose metabolism is compromised [34], potentially addressing the bioenergetic deficiencies in several physiological and mental disorders [35, 36]. In this sense, Augustin et al. [37] reported a pivotal role of ketones directly inhibiting glutamate receptors (AMPA receptors) and altering cell energetics through mitochondrial biogenesis. Interestingly, KD therapy also induces an epigenetic mechanism by means of DNA methylation [38].

Although a low-carbohydrate, high-fat, and high-protein diet, like KD, could be considered unhealthy for individuals with obesity, diverse studies have shown its effectiveness in treating this condition [39]. Lowering carbohydrate consumption has also been shown to result in substantial reductions in cholesterol, triglycerides, and diastolic blood pressure levels, while simultaneously raising high-density lipoprotein (HDL) levels [40]. KDs provide benefits through several mechanisms, such as appetite diminishment associated with greater levels of cholecystokinin, glucagon-like peptide 1, and ghrelin, or appetite suppression promoted by the ketones themselves. In short, it can be hypothesized that the results of KD in obese patients may also be related to its efficacy in increasing fat consumption and lipolysis while decreasing lipogenesis. In addition, KD inhibits gluconeogenesis in the liver by a decrease in insulin and an increase in glucagon, which then leads to a higher rate of resting energy expenditure [41].

By lowering glucose levels, KDs also restrict the metabolism of cancer cells, which are unable to effectively utilize KDs as an energy source [42]. Furthermore, KDs induce low glucose levels with an inhibition of the lactate/pyruvate cycle, thereby blocking neovascularization, hypoxia-induced epidermal growth factor activation, and angiogenesis [42]. Elevated KB levels inhibit NLRP3 inflammasome, limiting inflammation, which is central to cancer pathogenesis [43].

Gut microbiome modulation

With regard to the mechanisms through which dietary interventions operate, the potential mediating role of the gut microbiome is essential. The bacteria ecosystem within the gastrointestinal tract interacts with the diet consumed even before nutrients and other food-derived compounds enter the bloodstream [10]. It is possible to argue that various effects of the KD therapy may be mediated by the gut microbiome, either directly through metabolites produced by the microbes, or indirectly by influencing the activity of the enteric nervous system [44, 45]. Several studies have shown that KD plays a significant role in the composition and function of the gut microbiome [46]. Kim et al. [47] showed that a diet rich in fats and carbohydrates increases inflammation and pro-inflammatory cytokines through the TLR4 signaling pathway. Other authors found various changes in the bacterial composition of the gut, characterized by a reduction in members of the Bacillota phylum and an increase in members of the Bacteroidota phylum, in patients with obesity that were subjected to an isocaloric very-low-calorie KD (VLCKD) [48].

In animal models, Ma et al. [49] reported a change in the gut microbiome of mice after 4 months of KD feeding. These authors found an increase in the abundance of short-chain fatty acids (SCFA)-producers, such as *Akkermansia muciniphila* and *Lactobacillus*, and a decrease in the pro-inflammatory bacteria *Desulfovibrio* and *Turicibacter*. Similar results were found in a study of a mouse model of autism spectrum disorder (ASD) fed with a KD [50]. Interestingly, the KD decreased total cecal and fecal microbes in mice by an average of 78% and 28% respectively, probably due to the low amount of carbohydrates in the KD. In fecal samples, the abundance of *Akkermansia*, *Bifidobacterium*, *Lactobacillus*, and *Roseburia* decreased, whereas the members of the *Enterobacteriaceae* family, as well as of the genera *Bacteroides*, *Clostridium*, and *Prevotella* increased. In another study performed by Olson et al. [51], it was found that the KD induced significant changes in the gut bacteriome of mice, with a decrease in its α-diversity and in the abundance of the genera *Allobaculum*, *Bifidobacterium*, and *Desulfovibrio,* and with an increase in the abundance of the genera *Akkermansia*, *Parabacteroides*, and *Sutterella*, and also in members of the family *Erysipelotrichaceae*. These authors proposed that this dysbiosis may be correlated with seizure protection, including reductions in systemic gamma-glutamylated amino acids and elevated hippocampal GABA/glutamate levels, and also suggested diet- and microbiota-dependent alterations in serum ketogenic amino acids, as well as links between amino acid importation and brain GABA levels.

Several studies on the effects of KDs on the gut microbiome have been conducted in humans [8, 52], mainly in refractory epilepsy and cognitive disorders. For example, no statistically significant differences in Bacillota and Bacteroidota were reported in response to 3 months of KD consumption in patients with glucose transporter 1 deficiency syndrome. However, fecal microbial profiles revealed a significant increase in *Desulfovibrio* spp., a group of bacteria involved in exacerbating the inflammatory state of the intestinal mucosa [53]. Xie et al. [54], investigating patients with refractory epilepsy and healthy infants to know how

KD alters the gut microbiome, found that the diet produced a decrease in the genera *Cronobacter*, *Erysipelatoclostridium*, *Streptococcus*, *Alistipes*, *Ruminiclostridium*, *Barnesiella*, and *Enterococcus*, and an increase in the genera *Bacteroides* and *Prevotella*. In a study by Lindefeldt et al. [55], involving children with severe epilepsy, no significant changes were observed in the α-diversity of fecal microbiota. Nevertheless, there was a significant reduction in the relative abundance of *Bifidobacterium*, *Dialister*, and *Eubacterium*, along with an increase in *Escherichia* among children fed with KD. Using a modified Mediterranean-KD in subjects with mild cognitive impairment, Nagpal et al. [45] identified a decrease in the abundance of *Bifidobacterium* spp. and *Lachnobacterium* spp. in their gut, whereas *Akkermansia* spp., *Slackia* spp., and members of the *Christensenellaceae* family showed increased levels.

Interestingly, Ang et al. [56] conducted a study in both animal and human models, finding that KD intake led to decreased levels in members of Actinomycetota, *Lactobacillus* spp., and *Bifidobacterium* spp. In addition, the authors suggested that the KD could serve as a therapeutic approach to control autoimmune diseases, given its role in reducing pro-inflammatory Th17 cells. However, a potential downside of low carbohydrate diets, such as KD, is the decrease in *Bifidobacteria*, which has been positively associated with human health [57], although in a study it has been reported an increase of this specific bacterial genus [54]. Moreover, further evidence indicates that KD could also change the gut microbiome (increase in *Bilophila wadsworthia*), potentially affecting cognitive functioning, due to alterations in hippocampal regions and gene expression [58].

Effects of KDs on mental health

KD stabilizes neural networks, improves neuroplasticity, and has direct benefits in brain bioenergetics, which are related to several mental disorders [59, 60]. These effects of the KD confer health benefits by alleviating the symptoms of several neuropsychiatric and psychological conditions, such as epilepsy, anxiety, depression, schizophrenia, bipolar disorder, ASD, and certain neurodegenerative diseases [29, 61–67].

Epilepsy

Epilepsy is a neurological disorder characterized by recurrent seizures caused by abnormal neuronal activity and the KD has shown effectiveness as an alternative treatment by influencing biochemical processes, including cellular substrates and mediators of neuronal hyperexcitability, although it remains unclear whether its success is due to a single mechanism or multiple factors [22, 23]. KBs, such as BHB, have been implicated as mediators of the anti-inflammatory, anti-seizure, and neuroprotective effects associated with KD therapy [68, 69]. In neuronal cells, BHB can compete with glucose for energy production by inhibiting glycolytic flux upstream of pyruvate kinase [70], thereby diverting ketones into oxidative metabolism within the brain and increasing the ability to synthetize amino acids and GABA [71]. BHB has been recognized as an important effector of the positive outcomes of KD therapy because of several aspects: (i) BHB supports synaptic vesicle recycling, a mechanism with possible anticonvulsant outcome [72]; and (ii) BHB has a direct effect by acting as an endogenous ligand of the hydroxyl-carboxylic acid receptor 2 (HCA2), whose activation on a subset of macrophages induces a neuroprotective phenotype dependent on prostaglandin D2 production [68].

MCTs from KD, such as valproic, heptanoic, octanoic, and decanoic acids, have been widely used in refractory childhood epilepsy treatment, due to their improved anti-seizure efficacy and reduced toxicity [37, 73]. Heptanoic acid can provide energy for the tricarboxylic acid cycle and can lead to increased glutamine levels in the brain, indicating a potential role in the glial metabolism of heptanoate [74]. Decanoic acid, in contrast to octanoic acid, improves mitochondrial biogenesis and increases the transcription of genes involved in fatty acid metabolism, while downregulating genes related to glucose metabolism [75, 76]. In addition, MCTs influence astrocyte metabolism by supplying lactate and ketones as energy sources to adjacent neurons through the glial/neuronal shuttle system [77]. MCTs also impact amino acid metabolism, leading to elevated brain tryptophan levels, which are linked to decreased excitability in the hippocampal region [78]. Chang et al. [79] found that decanoic acid directly decreases neuronal excitability

by inhibiting AMPA receptor activity. These results indicate that decanoic acid may serve as a potent anticonvulsant mechanism of MCTs derived from the KD, based on its direct inhibition of excitatory neurotransmission.

KD therapy produces an anti-inflammatory activity and antioxidant effects that exert a relevant function in the pathophysiology of epilepsy via the regulation of peroxisome proliferator-activated receptors (PPAR), transcription factors implicated in mitochondrial biogenesis and in the control of genes involved in these pathways [27, 28, 80]. KD therapy generates cytochrome P450-dependent hydroxylation of reactive lipid species, a mechanism that may contribute to the anti-inflammatory properties of KD therapy [81]. In addition, KD therapy was found to reverse epilepsy progression, and to delay the onset of severe seizures [38]. In animal models, as above mentioned, a relationship between KD therapy and epigenetic mechanisms has been found, as an increase in DNA methylation is linked to chronic epilepsy in rats, and KD therapy also reduced seizure progression and mitigated DNA methylation-mediated shifts in gene expression, increasing adenosine that blocks DNA methylation [82–84].

Several systematic reviews and meta-analysis have been performed in recent years on the use of KDs (KD, MAD, MCTD, and LGIT) for the treatment of epilepsy and its symptoms [22, 66, 85]. Table 1 shows recent randomized controlled trials (RCT) and retrospective studies in humans on the effects of KDs therapy on different types of epilepsy.

Table 1. Human studies on the effects of ketogenic diets therapy on different types of epilepsy

Authors/Country	Intervention characteristics	Main findings
Sharma et al. [86] /India	• *N* = 95 children (2–14 years old) with drug-refractory epilepsy. • *N* = 46 MAD, *N* = 49 controls, 3 months, RCT.	MAD was found to be effective and well tolerated in children with drug-refractory epilepsy.
Wibisono et al. [87] /Australia	• *N* = 48 children (mean 3.8 years old) with intractable epilepsy. • KD, MCT, and MAD treatment, 9 years, retrospective study.	Lower rates of side effects were scored for MAD. The three KDs were comparably effective in seizure control and tolerability.
Kim et al. [88]/Korea	• *N* = 104 patients aged 1–18 years old with refractory epilepsy. • *N* = 53 MAD, *N* = 51 KD, 6 months, RCT.	MAD may be considered as the primary choice for the treatment of intractable epilepsy in children. KD is more suitable as diet therapy in children < 2 years of age.
Lambrechts et al. [89] /The Netherlands	• *N* = 48 patients aged 1–18 years old with refractory epilepsy. • *N* = 26 KD, *N* = 22 control, 4 months, RCT.	KD is an effective therapy for children and adolescents with refractory epilepsy.
Kverneland et al. [90] /Norway	• *N* = 62 patients aged > 16 years old with at least 3 seizures/month. • *N* = 28 MAD, *N* = 34 control, 3 months, RCT.	A significant reduction in seizure frequency was achieved with the MAD treatment compared to control.
McDonald et al. [91] /USA	• *N* = 80 adult patients > 18 years old with drug-refractory epilepsy and at least 4 seizures/month. • MAD and MAD + KetoCal, 2 months, RCT.	MAD significantly reduced seizures at the end of the treatment.
Park et al. [92]/Korea	• *N* = 16 children (mean age of seizure onset 8 years) with super-refractory status epilepticus (SRSE). • KD treatment. 12 years, retrospective study.	KD may be a feasible and safe therapeutic approach for SRSE patients in reducing the frequency of seizures.
Sondhi et al. [93]/India	• *N* = 158 children (1–15 years old) with 4 or more seizures/month. • *N* = 52 MAD, *N* = 52 KD, *N* = 54 LGIT, 6 months, RCT.	LGIT diet showed a balance between seizure reduction and relatively fewer adverse events compared to MAD and KD.
Shegelman et al. [94] /USA	• *N* = 60 patients with chronic epilepsy	Lower seizure frequency was significantly associated with anxiety symptoms. MAD had a positive input on

Table 1. Human studies on the effects of ketogenic diets therapy on different types of epilepsy (*continued*)

Authors/Country	Intervention characteristics	Main findings
	(19–75 years old). • *N* = 36 MA, *N* = 24 control, 3 months, retrospective study.	psychological state independent of seizure reduction or KB production.
Rafli et al. [95] /Indonesia	• *N* = 31 children (2–18 years old) with intractable epilepsy. • MAD treatment for 6 months, pilot experimental study.	MAD reduced the seizure frequency by 50% in the first month, 62% in the third, and > 83% in the sixth month.

KD: ketogenic diet; MAD: modified Atkins diet; MCT: medium-chain triglyceride; LGIT: low glycemic index therapy diet; RCT: randomized controlled trial; KB: ketone body

According to the diverse outcomes obtained by the studies specified in Table 1, KD and its variants produced successful and well-tolerated effects in individuals with refractory epilepsy, with significant improvements in seizure control and minimal side effects, particularly in children.

Mood, anxiety, and depression

Mood disorders, including anxiety and depression, are a group of prevalent mental conditions often linked to metabolic dysfunctions and neuroinflammation, which may influence the development and persistence of symptoms [60, 96]. Substantial enhancements in depressive and psychotic symptoms, in subjects with severe mental disorders who underwent KD, were reported in a retrospective study [97]. Likewise, Adams et al. [98] also noted an important improvement in mood in outpatients with type 2 diabetes who were treated with a KD for 2 years. More recently, Calabrese et al. [62] and Garner et al. [99] reported that KD improved mood, anxiety, and depression symptoms in participants. Conversely, Iacovides et al. [100] reported no significant differences in cognitive performance, mood, or subjective sleep quality, between the two groups of participants (KD individuals and isocaloric high-carbohydrate low-fat diet individuals). Thus, while various studies suggest the potential of KD to improve mood and reduce symptoms of anxiety and depression, conflicting findings underscore the need for further research to clarify its efficacy and identify the factors influencing individual responses to this dietary intervention.

Bipolar disorder and schizophrenia

Bipolar disorder and schizophrenia are complex psychiatric conditions with distinct diagnostic criteria and etiologies involving genetic and environmental factors, in which gastrointestinal inflammation and gut-brain axis alterations may contribute to their pathophysiology [61, 96]. In fact, while the precise pathophysiology of bipolar disorder and schizophrenia is not fully understood, evidence indicates that disrupted energy metabolism and associated oxidative stress are critical factors in the expression of symptoms [101]. Campbell and Campbell [102] proposed that KD may alleviate symptoms of bipolar disorder by circumventing the effects of mitochondrial dysfunction. Later, in two pilot studies, Needham et al. [103] and Sethi et al. [104] found that the adverse effects of bipolar disorder were reduced by the KD application.

Administration of KD or BHB efficiently regularized behavioral impairments in a hypo-glutamatergic animal model of schizophrenia [105–107]. Results from a human case study [108] showed that KD improved symptoms and quality of life in individuals with schizophrenia. Sethi et al. [104] reported improvements in several psychiatric symptoms related to schizophrenia and bipolar disorder, as well as in other metabolic functions. In addition, Bohnen et al. [109] designed a pilot trial protocol to evaluate the effect of a ketogenic mimicking diet (ketone esters combined with a supplementation consisting of a low glycemic index diet) on mood, neural network stability, and biomarker outcomes in subjects with bipolar disorder, reporting positive findings.

Autism spectrum disorder

ASD is a developmental brain disorder characterized by stereotyped behavior and deficits in communication and social interaction, with its complex pathology and etiology implicating genetic factors,

immune dysregulation, environmental exposures, and gut microbiota alterations [96]. Several lines of evidence implicate mitochondria in the pathophysiology of ASD [110]. For this reason, KD could be a fruitful therapy for ASD since it enhances the core symptoms of ASD, potentially mitigating its comorbidities such as seizures [65]. In this regard, various studies on the therapy of KD for ASD have been conducted in recent years [111, 112], obtaining promising results. Nevertheless, further research is needed to better understand its efficacy and mechanisms in treating core symptoms and comorbidities.

Neurodegenerative diseases

Neurodegenerative diseases are commonly characterized by neuroinflammation and synaptic damage, with gut microbiota dysbiosis increasingly recognized as a factor in their pathophysiology [96]. Research suggests that KDs may play a role in neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), because hypometabolism in neurodegenerative diseases is ameliorated by KBs [63]. The mechanism underlying the efficacy of KDs remains unclear, but some evidence suggests the normalization of aberrant energy metabolism [64]. In addition, the antioxidant and anti-inflammatory activities, as well as the mitochondrial function of KDs, may improve health biomarkers and symptoms of the pathophysiology of AD and PD [32, 113]. Almost all studies performed on the influence of various KDs on neurodegenerative diseases reported benefits in the prevention of cognitive decline [113–118], except in the case of the study by Henderson et al. [119], who found that caprylic/capric triglyceride did not improve cognition or functional ability in AD patients. The authors suggested that the low KB formation of this diet may explain this unsuccessful result. Consequently, the potential of KDs to alleviate neuroinflammation and metabolic disruptions in both AD and PD is promising, but further investigation is required to evaluate their viability as therapeutic options. Table 2 summarizes recent studies on the role of KDs in various human psychological and neuropsychiatric disorders.

Table 2. Role of the ketogenic diets therapy in several mental disorders

Authors/Country	Intervention characteristics	Instruments	Outcomes
Calabrese et al. [62]/USA	Depression: *N* = 3 adults (32–36 years old) with MDD and GAD. Treatment with KD for 12–16 weeks.	GAD-7, PHQ-9.	Two from three patients achieved remission in MDD and GAD within 12 weeks of KD treatment.
Danan et al. [97] /France	Depression, bipolar disorder, and schizophrenia: *N* = 31 adults. Treatment with KD for 248 days.	HDRS, MADRS, PANSS.	The KD treatment for patients with refractory mental illness was feasible, well-tolerated, and associated with significant improvements in depression and psychosis symptoms.
Adams et al. [98] /USA	Depression: *N* = 262 adults (21–65 years old) with diabetes type 2. Treatment with carbohydrate restriction diet for 2 years.	CESD	Subclinical depressive symptoms decreased over the first 10 weeks and reductions were maintained out to 2 years with the tested diet.
Garner et al. [99] /United Kingdom	Mood: *N* = 147 patients (> 18 years old). Treatment with KD for 8 months. Depression and anxiety: *N* = 276 (> 18 years old). Treatment with KD for 6 months.	BL-VAS, DASS-21.	KD was associated with higher self-reported mental and emotional well-being behaviors, including calmness, alertness and contentedness (improved mood). In addition, individuals who consumed a KD were less anxious and depressed.
Iacovides et al. [100]/South Africa	Mood: *N* = 11 healthy subjects (mean age 30 years old). Treatment with KD and an isocaloric diet (HCLF) for 3 weeks.	Cogstate, PSQI.	The results suggest that 3 weeks of sustained nutritional ketosis had no effect on cognitive performance, mood, or subjective sleep quality.
Needham et al. [103]/United Kingdom	Bipolar disorder: *N* = 20 euthymic individuals with bipolar disorder (18–70 years old). Treatment with KD for 6 weeks.	BDI, YMRS, ALS, WTRUQ.	The adverse events in the majority of participants were generally mild and modifiable.
Sethi et al. [104] /USA	Bipolar disorder and schizophrenia: *N* = 23 (18–75 years old). Treatment with KD for 4 months.	BPRSS, CGI.	Participants with schizophrenia showed a reduction in BPRSS, and the severity of CGI improved.
Longhitano et al. [107]/Australia	Bipolar disorder, schizoaffective disorder, and schizophrenia: *N* = 100 (> 18 years old). Treatment with modified KD for 14 weeks.	PANSS, BDI, YMRS, ALS, CCB.	The modified KD therapy was well tolerated and improved psychiatric and metabolic outcomes. The authors suggested a correlation between the levels of ketones and metabolic, cognitive and psychiatric improvements.

Table 2. Role of the ketogenic diets therapy in several mental disorders (*continued*)

Authors/Country	Intervention characteristics	Instruments	Outcomes
Palmer et al. [108] /USA	Schizophrenia: *N* = 2 adults (39 and 82 years old). Treatment with KD for 2 weeks.	PANSS	The cases suggest that KD may be an effective treatment for schizophrenia and for restoring function in life.
Lee et al. [111] /USA	Autism: *N* = 15 children with ASD (2–17 years old). Treatment with a modified KD (gluten free) supplemented with MCT for 3 months.	ADOS-2, CARS.	The modified diet is a potentially beneficial treatment tool to improve the features of ASD.
Żarnowska et al. [112]/Poland	Autism: *N* = 1 child (6 years old). Treatment with KD for 16 months.	WISC-R, CARS.	KD improved the behavior and intellect of the subject.
Tidman et al. [113] /USA	Parkinson: *N* = 1 PD patient (53 years old). Treatment with KD for 24 weeks.	CESDR, PAS, UPDRS.	KD results in the elevation of blood ketones that provide an enhanced mood, motivation and sleep quality, reduced levels of anxiety, and improved cognitive functions while reducing PD symptoms.
Phillips et al. [114] /New Zealand	Parkinson: *N* = 38 PD patients (40–75 years old). Treatment with KD or low-fat KD for 8 weeks.	UPDRS, MoCA.	Both diet groups significantly improved motor and non-motor symptoms; however, the KD group showed greater improvements in non-motor symptoms.
Neth et al. [115] /USA	Alzheimer: *N* = 20 AD patients (11 with subjective memory complaints and 9 with mild cognitive impairment). Treatment with modified Mediterranean-KD (MMKD) for 6 weeks.	SMC, MRI.	All participants improved metabolic indices following MMKD. This diet has been associated with decreased tau and it is adequate in the prevention of cognitive decline.
Ota et al. [116] /Japan	Alzheimer: *N* = 20 AD patients (mean age 73.4 years). Treatment with MCT for 12 weeks.	MMSE, ADAS-Cog.	Diet produced significant improvement in verbal memory and processing speed in AD patients.
Phillips et al. [117] /New Zealand	Alzheimer: *N* = 21 hospitalized patients with AD (mean age 73.4 years old). Treatment with modified KD or low-fat KD for 10 weeks.	ACE, QoL-AD, ADCS-ADL.	AD patients who consumed modified KD increased ADCS-AD and QoL-AD scores.
Brandt et al. [118] /USA	Alzheimer: *N* = 9 patients with AD. Treatment with MAD for 12 weeks.	MCS	MAD participants increased MCS scores, enhanced episodic memory, and patient-reported vitality in very early AD.
Henderson et al. [119]/USA	Alzheimer: *N* = 413 mild-to-moderate AD patients. Treatment with AC-1204 (caprylic triglyceride) for 24 weeks.	ADAS-Cog, ADCS-ADL.	The formulation AC-1204 (caprylic triglyceride) failed to improve cognition or functional ability in AD patients.

KD: ketogenic diet; MCT: medium-chain triglyceride; MAD: modified Atkins diet; MDD: major depression disorder; GAD: generalized anxiety disorder; ASD: autism spectrum disorder; PD: Parkinson's disease; AD: Alzheimer's disease; ACE: Addenbrookes Cognitive Examination; ADAS-Cog: Alzheimer's disease Assessment Scale-Cognitive Subscale; ADCS-ADL: Alzheimer's disease Cooperative Study-Activities of Daily Living Inventory; ADOS-2: Austism Diagnostic Observation Schedule-2; ALS: Affective Lability Scale; BDI: Beck's Depression Inventory; BL-VAS: Bond-Lader Visual Analog Scales; BPRSS: Brief Psychiatric Rating Scale Scores; CARS: Childhood Autism Rating Scale; CCB: Cambridge Cognitive Battery; CESD: Center for Epidemiologic Studies Depression Scale; CESDR: Center for Epidemiologic Studies Depression Scale-Revised; CGI: Overall Clinical Global Impression; Cogstate: Psychological Computer-based Test Battery; DASS-21: Depressive Anxiety Stress Scale-21; GAD-7: Generalized Anxiety Disorder Scale-7; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; MCS: Memory Composite Score; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging; PANSS: Positive and Negative Syndrome Scale; PAS: Parkinson's Anxiety Scale; PHQ-9: Patient Health Questionnaire-9; PSQI: Pittsburg Sleep Quality Index; QoL-AD: Quality of Life in Alzheimer's disease; SMC: Cognitive Change Index; UPRS: United Parkinson's Disease Rating Scale; WISC-R: Wechsler Intelligence Scale for Children-Revised; WTRUQ: Within Trial Resource Use Questionnaire; YMRS: Young Mania Rating Scale

Discussion

The potential of dietary interventions as a therapeutic tool in the treatment of diverse health conditions is immense and widely recognized [10, 120]. This review summarizes studies related to the effects of KD therapy on various physiological and mental disorders, as well as those on the changes provoked by this diet on the composition and function of the gut microbiome. From the studies reviewed, it is clear that KD exerts a reduction in seizure frequency in refractory epileptic patients; therefore, the diet and its modifications may be considered as the primary feeding choice for intractable epilepsy in children. In addition, KDs support neural stability, neuroplasticity, and brain bioenergetics [121], prompting preclinical

and clinical trials to explore their capability in treating psychiatric, psychological, and neurodegenerative disorders [122].

KD plays a neural protective role through various mechanisms at the mitochondrial level, including increased levels of uncoupling proteins, enhanced antioxidant activity [reduced production of reactive oxygen species (ROS)], and ATP synthesis in the brain and brain mitochondria [123]. KD exerts its antioxidant effects on mitochondria mainly by regulating the function of mitochondrial respiratory complexes, decreasing ROS, and increasing antioxidant levels [124].

Several studies have reported that KDs and KBs confer neuroprotective effects by supplying alternative energy substrates to neurons and enhancing mitochondrial structure and function [123]. Additionally, KBs and KDs exhibit positive impacts by reducing oxidative stress and apoptosis [125, 126], promoting autophagic flux, and regulating gene expression and other cellular functions through epigenetic and post-translational modifications of histones and non-histone proteins [123]. KBs and KD also suppress neuroinflammation, and modulate neurotransmitter systems and the gut microbiota [123, 127].

Collectively, the encouraging findings from existing preclinical studies, case reports, and uncontrolled clinical trials suggest a clinically significant potential for KD therapy in the treatment of mental illnesses of varying severity, providing hope to millions of individuals globally affected by these conditions. However, randomized controlled clinical trials are necessary to determine the impact of the ketotic metabolic state on the desired outcomes. Additionally, extensive long-term clinical research on mental disorders is essential to assess the adverse effects, efficacy, and sustainability of the KD. Furthermore, addressing potential methodological limitations in studies on dietary effects is pivotal, as such limitations can compromise the validity of results, similar to issues observed in research on other dietary patterns [128, 129].

Considering the potential of KD in treating neuropsychiatric and psychological disorders [96], understanding its impact on the gut microbiome is crucial. Changes in microbiome composition and function may underlie some of the observed therapeutic effects, providing insights into how KD modulates brain function and mental health. The field of omics encompasses a range of high-throughput methodologies, including genomics, transcriptomics, proteomics, and metabolomics, along with their corresponding meta-omics derivatives, such as meta-proteomics, metagenomics, and meta-transcriptomics [130]. These methodologies will constitute an essential strategy to know the influence of the gut microbiome and its metabolites on the effects of the KD on mental disorders. Multi-omics approaches, in fact, could enhance our understanding of the changes and interactions occurring within the gut microbial community following the consumption of a diet, such as KD [131]. Ultimately, integrating these advanced techniques could lead to novel insights into the therapeutic potential of dietary interventions in mental health and support the development of more effective, personalized treatment strategies.

Beyond individual metabolic effects, the KDs seem to show important implications for public health, clinical practice, and dietary policy. Given its potential to influence physiological and mental health, KDs could be particularly beneficial for populations with limited success using conventional diets, especially individuals with metabolic syndrome, diabetes, epilepsy, and neuropsychiatric disorders. This dietary approach also has potential relevance for aging populations vulnerable to neurodegenerative diseases, where the neuroprotective properties of KDs may improve quality of life and reduce healthcare burdens, and may also complement other interventions with relatively limited effectiveness [132]. Additionally, practitioners in mental health, neurology, endocrinology, and nutrition could benefit from a robust understanding of KD principles to apply in therapeutic contexts, while healthcare systems, public health organizations, and policymakers should consider the KDs in the context of broader dietary frameworks and interventions. Comparative studies with other diet plans, such as Mediterranean or vegetarian diets, could be essential to elucidate the long-term sustainability of KDs, as well as their efficacy and feasibility for diverse populations. Ethical and educational initiatives will be necessary to ensure it is accessible, equitable, and aligned with individual health needs, maximizing its therapeutic potential while acknowledging the challenges of widespread adoption. In this respect, given that the KD relies heavily on animal-based fats and proteins, raising critical concerns for both environmental sustainability and animal

well-being, its application should be restricted to specific populations with a demonstrated therapeutic need.

This narrative review presents several limitations: (i) the studies reviewed encompass different types of KDs, making it difficult to generalize the reported results; (ii) many of the studies included both animal models and human subjects, which complicates direct comparisons and the establishment of a clear relationship between KDs and the gut microbiome; (iii) the microbiological methodologies employed in the reviewed studies varied widely, with different omics techniques potentially offering varying degrees of precision in bacterial taxonomy, which may explain the contradictory findings observed; (iv) most of the studies focused on short-term KD intake, and there has been limited investigation into long-term dietary effects and follow-up; (v) the inclusion of studies with small sample sizes, either in terms of participants or animals, undermines the statistical power of the reported results; (vi) the heterogeneity of the included studies in terms of design, sample characteristics, and methodology may have influenced the ability to make direct comparisons, thereby limiting the interpretation of the findings; and (vii) several of the studies reviewed focused on patients with epilepsy or other medical conditions, who already exhibit gut microbiome alterations inherent to these disorders, which constitute a significant source of bias and confounding factors.

Conclusions

In general terms, KDs promote weight loss, enhance insulin sensitivity, and may reduce dyslipidemia. That is why KDs are used as a therapeutic tool for a variety of metabolic-related conditions, including obesity, diabetes, and skin diseases. In addition, the beneficial effects of KDs on epilepsy symptoms, particularly in refractory epilepsy, are well known due to the antiepileptic efficacy and reduced toxicity of these diets. By raising KBs, KDs boost mitochondrial function, reduce oxidative stress, modulate autophagy, and impact neurotransmitters and neuroinflammation. KDs also offer benefits by reducing appetite and enhancing fat consumption and lipolysis while decreasing lipogenesis. Furthermore, KDs boost gluconeogenesis, leading to increased energy expenditure. Their low-glucose composition has the potential to restrict cancer cell metabolism and inhibit neovascularization, hypoxia response, and angiogenesis. KDs also have the capability of shaping the gut microbiome, potentially managing autoimmune diseases by reducing inflammation, despite they may lower beneficial bacteria levels. The alteration of the gut microbiome composition produced by KDs depends on the KD type, and existing controversial results of the consequence of this dysbiosis. In this regard, it has been reported that the administration of these diets exacerbated the inflammatory state of the intestinal mucosa, whereas it has been also noted that these diets induce a reduction of pro-inflammatory Th17 cells. In mental health, KDs seem to stabilize neural networks, enhance neuroplasticity, and improve brain energy use, with possible benefits for neurodegenerative diseases, as well as for other psychiatric and psychological disorders. Within this context, KDs appear to exert an influence due to their antioxidant properties and low carbohydrate content, which open a new window for the implementation of these diets in dietary protocols within hospital and geriatric settings. Thus, KDs may serve as promising tools both as adjuvant therapies and as dietary patterns for specific populations across physiological, metabolic, and mental conditions. However, more randomized, long-term studies are required to assess their efficacy, sustainability, and safety, including methodological rigor to strengthen findings on dietary impacts.

Despite the potential benefits and growing attention focused on KDs, it remains premature to draw definitive conclusions regarding their overall feasibility for widespread clinical application. Their use should be targeted at specific medical conditions rather than promoted as a general dietary pattern. Moreover, ethical and environmental considerations should not be overlooked, as KDs often rely on animal-derived resources. In this respect, KDs do not necessarily have to be based on animal products, as the key principle is to maintain a low carbohydrate intake while prioritizing a sufficient supply of healthy fats, regardless of their source.

Abbreviations

AD: Alzheimer's disease

ASD: autism spectrum disorder

BHB: β-hydroxybutyrate

GABA: γ-aminobutyric acid

HCA2: hydroxyl-carboxylic acid receptor 2

KBs: ketone bodies

KD: ketogenic diet

LGIT: low glycemic index therapy

MAD: modified Atkins diet

MCTD: medium-chain triglyceride diet

MCTs: medium-chain triglycerides

PD: Parkinson's disease

ROS: reactive oxygen species

Declarations

Author contributions

ABR: Conceptualization, Writing—original draft, Writing—review & editing, Supervision. JJB: Conceptualization, Investigation, Writing—original draft. Both authors read and approved the submitted version.

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Both authors declare that they have no conflicts of interest.

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