




## REVIEW PAPER

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# Ketogenic diet as possible therapy of autism spectrum disorder – review and implication

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### ABSTRACT

Autism spectrum disorder (ASD) has become widespread neurodevelopmental disorder, which currently can be treated with only few therapeutic options. Furthermore, their effectiveness is limited therefore novel treatment strategies for ASD are needed. This review seeks to address this need by discussing a ketogenic diet (KD) in the context of ASD therapy. KD effects have been examined in animal and human studies. They indicate effectiveness of KD by improving autistic features. Moreover, animal studies have revealed clinically useful information about caloric restriction component of KD, which is not necessary to achieve therapeutic effects. Significantly administration of KD but not  $\beta$ -hydroxybutyrate or acetone has a therapeutic effect on social interactions. Human studies are scarce, however previous researches imply KD as an effective treatment at least in certain types of autism. KD in an altered form as: modified Atkins diet (MAD), ketogenic gluten-free diet with supplemental medium-chain triglyceride (MCT), and John Radcliffe ketogenic diet is an alternative to classic KD. These variants provide better quality of nutrition and are less strict, thus less difficult to maintain. KD is described as safe with limited, easily manageable adverse effects. Taken together human and animal studies would seem to suggest that KD will become part of ASD treatment. However, in order to determine accurate recommendations for all ASD patients, further studies are required.

**Keywords:** autism spectrum disorder, ketogenic diet, autism, dietary approach.

## Introduction

ASD is a neurodevelopmental disorder of unknown etiology, which is characterized by impairment in reciprocal social interactions and behavior [1]. The term “spectrum disorder” refers to the conditions and their specific symptoms that differ among affected individuals, ranging from severely impaired, low-functioning to mildly affected patients [1]. ASD is typically diagnosed during early childhood by behavioral abnormalities such as hyperactivity, aggression, repetitive behaviors and lack of social communication. The etiology is still not understood, howev-

er some risk factors have been implicated in the pathogenesis, including genetics, inborn error of metabolism (IEM), pre/peri/post-natal factors, and interactions between them [2]. These factors affect brain maturation by changing neuroanatomy, synaptogenesis, axon motility and functioning, which, in turn, results in dysfunctional neural networks engaged in socioemotional processing [2]. As shown in neuroimaging studies, the pathophysiology of ASD can generate micro- and macro-effects with disorganized cortical layers, different than normal ratio of short- to long-diameter axons, and overgrowth of grey matter in cortical and subcortical regions in early develop-

ment of the brain [2]. It has been proposed that the disease-associated lesions in amygdala and nucleus accumbens play crucial role in the development of behavioral symptoms of ASD [3].

While there is no cure currently available for patients with ASD, the right support can make an enormous difference in patients' quality of life and ability to function in the society [1, 4]. At present, there is a growing interest in possible dietary intervention as a potential management for ASD. KD appears to be one of the promising therapeutic options for this disorder, however, prospective controlled trials with large sample size are needed for establishing an official recommendations. The "classic" ketogenic diet, originally developed by Wilder in 1921, is a special high-fat, low-carbohydrate diet described by ratio 4:1 (energy from fat: energy from carbohydrate and protein) [5], which has been used successfully to treat drug-resistant epilepsy [6, 7]. Today, several variations of KD have been introduced for treatment purpose, including Radcliffe Infirmary diet, which represents a combination of the traditional and MCT diets, or MAD characterized by fewer protein and caloric restriction [8, 9].

Although the KD is linked with a long list of possible side effects (such as metabolic abnormalities, gastrointestinal symptoms, carnitine deficiency, hypercholesterolemia, renal calculi, cardiac abnormalities, higher risk of bone fractures, kidney stones, and decreased rate of growth), the risk of severe adverse effects is not high [10]. Regarding the clinical management of the KD, it is recommended to consider all pros and cons individually. Since the KD sets up lipids as the major energy source, the absolute contraindications are associated with fat metabolism disorders and include, among others, primary carnitine deficiency, carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency,  $\beta$ -oxidation defects, medium-chain acyl dehydrogenase deficiency, long-chain acyl dehydrogenase deficiency, short-chain acyl dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA deficiency, medium-chain 3-hydroxyacyl-CoA deficiency, pyruvate carboxylase deficiency, porphyria. The list of relative contraindications is brief and comprises: inability to maintain adequate nutrition, surgical focus identified by neuroimaging and video EEG monitoring, parent or caregiver noncompliance [10]. KD works through

several combined mechanisms that reduce neuronal excitability. Increased ketones production and restriction of glucose affect ion channels, enzymes, and variety of receptors in the central nervous system. KD additionally enhances adenosine level with concomitant inhibition of DNA methylation. These mechanisms, working together, improve mitochondrial function, alleviate oxidative stress, affect circadian activities and improve synaptic vesicle recycling. The final effects include anti-seizure, neuroprotective, and anti-inflammatory influence of KD [11]. More recently, the therapeutic use of KD in human and animal models of ASD has been studied with positive results. This paper presents selected important findings on the ketogenic diet effects and possible mechanistic insights in ASD affected individuals.

## Animal studies – different models, similar behavioral effects

Although large body of evidence indicates beneficial effects of KD for animal ASD treatment, there is much about mechanistic insights that remain unclear, however, some published reports can provide useful suggestions. Obviously, no single pathway is likely to explain the clinical effects of KD. Key mechanisms may include: improved mitochondrial function [12], regulation of neuronal membrane excitability [13], reduced inflammation [14], increased total quantity of bioenergetic substrates [15], or neuroprotection by sparing glucose [16].

Given that different environmental factors during pregnancy are associated with development of ASD in children, prenatal exposure to valproic acid (VPA) is widely used as a reliable animal model of ASD. The VPA-treated mice present, among others, abnormalities in play behavior (decreased number of play initiations/attacks), repetitive behavior, higher nociceptive threshold and bioenergetic dysfunction in mitochondria. It has been found that these abnormalities could be reversed, to some degree, with the KD [17]. KD treatment in prenatal VPA exposed rodents normalized dysfunctions in mitochondrial respiration and significantly improved social impairment [18]. Dai et al. tested protective effect of a ketogenic diet on ultrasonic vocalization, sociability, spatial learning and memory, and electroencephalogram seizures

in glut3 heterozygous null (glut3+/-) mice exhibiting features relevant to ASD. They observed KD-related partial restoration of social features and alleviation of seizure events in male subjects without affecting perturbed vocalization, spatial learning and memory. They have also found that neuroprotection of females results from higher circulating and cerebrospinal fluid ketone concentrations and/or lower brain Glut3 concentrations [19].

Testing mutant EL mice with comorbid epilepsy and ASD symptoms, Ruskin et al. have found a clear sex-related difference in response to the beneficial effects of KD. They used two ketogenic diet formulas: with a 6,6:1 and 3:1 ratio of fat: (carbohydrate + protein) and found that caloric restriction component of KD is not necessary to achieve therapeutic effects in this model. Feeding with both types of KD improved multiple measures of sociability and reduced repetitive behavior in female mice, with limited effects in males [20].

Complete understanding of sex-specific changes may provide an insight into unique factors that may contribute to the partial protection and lower prevalence of ASD in females [21].

A high fat, moderate protein, and low net-carb diet was also used in the experiments with BTBRT+Tf/J mice. These animals display behaviors consistent with diagnostic features for ASD (impaired social interaction and communication and increased repetitive behaviors). Rutskin et al. described improvement in behavioral symptoms of ASD, expressed by decreased self-directed repetitive behavior and better social communication, in ketogenic diet-fed BTBR mice [22]. Mychasiuk et al. observed positive effects of KD administration on ASD deficits associated with myelin formation and white matter development in BTBRT+Tf/J mice [23]. Additionally, based on spontaneous intrahippocampal EEGs and tests of seizure susceptibility, they found that behavioral improvements are dissociable from any antiseizure effect of KD.

Based on high-resolution intracortical microstimulation, findings from BTBR mouse model of ASD have documented imbalance in excitation to inhibition and aberration in cortical motor maps. Importantly, the KD appeared to be effective in reversing both of these abnormalities [24].

The two other studies have shown no significant effect of KD on tested brain parameters in BTBR model of ASD [25, 26]. Because abnormal

mitochondrial function of neurons plays crucial role in the pathophysiology of ASD and mitochondria itself represent the metabolic endpoint for dietary foodstuffs, these studies focused on examination of mitochondrial dynamics in BTBR mice after administration of KD. The first study was scheduled to determine whether KD induces changes in brain and liver protein O-linked- $\beta$ -N-acetyl glucosamine (O-GlcNAc), which patterning is usually abnormal in ASD epilepsy [25]. The second one, analyzed impact of KD on mitochondrial gene expression and proteins levels in the brain and liver [26]. Both experiments have shown tissue-specific effects of KD with evident changes (reduced global O-GlcNAc and increased mitochondrial turnover) in the livers and no disturbances in brain dynamics. This suggests that other than tested mechanisms are involved in beneficial activity of KD for BTBR mice.

Recently, it has been shown that ASD coexists with altered gut microbiota in a BTBR murine model of ASD [27, 28]. Although the exact mechanisms remain unknown, the therapeutic effectiveness of KD may partially result from the restoration of the correct gut microbial composition. This observation allows researchers to consider gut microbial abundance and diversity as a possible factor capable to mitigate some of the ASD symptoms in humans. However, further research investigating the microbiota in the context of dietary intake and severity of ASD is needed.

Another tested animal model of ASD is associated with mutations in the En genes. Mice with deletion of the En2 gene from birth demonstrate behavioral impairments typical for ASD due to the several anatomic changes in the cerebellum and hippocampal region of the brain and defects in monoamine system [29]. Verpeut et al. conducted experiments with En2 knockout mice exposed to KD from post-natal day 21 to 60. The early timing of dietary intervention was recognized as being important for the brain reorganization and maturation influenced by nutrition. Although 2 null mice (En2(-/-)) displayed no altered monoamine content in the forebrain regions, the increased frontal social contact and reduced grooming behavior were evident in response to KD intervention.

To weigh up the effects of KD and administration of an exogenous ketones, an interesting study was performed on wild type Long-Evans(LE) rat males, a model with behavioral characteris-

tics of autism spectrum disorder and comorbid epilepsy [30]. Authors compared behavioral outcomes following exposure to a ketogenic diet versus  $\beta$ -hydroxybutyrate or acetone administration and noted improvement in social interactions only in KD-fed animals. This suggests that therapeutic effect of the KD is more complex than simply raised  $\beta$ -hydroxybutyrate or acetone blood-levels.

A number of epidemiological studies have reported increased risk of ASD associated with maternal infection during pregnancy and maternal immune activation (MIA) hypothesis has been widely tested in animal models [31]. Using synthetic agents that induce MIA in mice, Ruskin et al. have demonstrated that male MIA offspring were significantly asocial in the three chamber sociability test, while female mice displayed normal and social behavior [32]. Within 3–4 weeks of KD treatment the lack of sociability in male offspring reversed completely and reduced MIA-elevated self-directed repetitive behavior was observed. This model seems to be of particular importance because it mimics clinically-common conditions whereby ASD incidence is increased by maternal infection during pregnancy in humans.

## Human studies

Current data indicate that at least certain types of autism respond to KD treatments in humans. At this time, with few therapeutic options, new treatment strategies for ASD are needed, but considering the possible adverse effects of KD, the intervention requires high-quality scientific evidence about effectiveness and safety. Therefore, ongoing studies are looking for an optimal, safe and well tolerated dietary modifications.

### Clinical benefits of ketogenic diets

El-Rashidy et al. designed a prospective clinical interventional study on 45 ASD children, aged 3–8 years, to compare the effect of MAD ( $n = 15$ ) and gluten-free and casein-free diet (GFCF) [33]. MAD is similar to the classic KD but is less restrictive, has no limit on calories or protein, and the lower overall ketogenic ratio does not need to be maintained in all meals. At 6-month follow-up, the Childhood Autism Rating Scale (CARS) and Autism Treatment Evaluation Test questionnaire (ATEC) showed significant improvements in both, MAD and GFCF-fed patients including speech,

social and cognition parameters. On the other hand, several systematic reviews focusing on pure GFCF in ASD reported inconclusive results and definitely further efforts must be made to identify the group of ASD patients who may be the best responders to this intervention [34,35]. In another clinical trial, Lee et al. used a modified ketogenic gluten-free diet with supplemental MCT in 15 patients aged 2 to 17 years [36]. After 3 months of observation, they reported significant improvements in CARS-2 and ADOS-2 (Autism Diagnostic Observation Schedule) items without restricted and repetitive behavior scores.

Beneficial effects of modified KD have been reported in a 1-year prospective uncontrolled study conducted on thirty children, aged 4–10 years, with autistic behavior [37]. Patients received the John Radcliffe ketogenic diet, which is a variation of the medium-chain triglyceride diet and, as reported by parents and caregivers, is less restrictive and easier to implement practically than classic KD. Moreover, to prevent adverse effects that may accompany KD administration, the diet was implemented in a 4-week intervals followed by 2 weeks break. Interestingly, such a regimen provided long lasting effects and the improvements persisted even after termination of the trial in 60% of study participants (18 out of 30 patients) with better response in mild cases of ASD.

Herbert and Buckley presented a case of 12 year old autistic girl with comorbid autism and epilepsy put on gluten-free casein-free KD [38]. In their remarkable case study, they described significant reduction in seizures and improved cognitive and behavioral function accompanied with successful management of morbid obesity subsequent to initiation of modified KD. The main rationale for using a casein-free, medium-chain-triglyceride-predominant ketogenic diet was to achieve ketosis with a much lower ratio than is typically needed and to provide better quality of nutrition (more calories were available for vegetable consumption) when compared with pure KD.

### Tolerability and adverse effects of KD

The concept that the ketogenic diet may be neuroprotective has raised the possibility to use it as an additional or alternative therapy among children with autistic behavior, especially those with epileptic events. To achieve the benefits of this

dietary management, patients need to be adhered to the prescribed KD for at least 6 months to 1 year [39]. A medical consequences of the ketogenic diet, in terms of side effects, may include constipation, diarrhea, vomiting, dehydration, kidney stones, slow growth, osteomalacia, cardiomyopathies, gout, hypocalcemia, hypomagnesemia, acidosis, vitamin D deficiency, hypoproteinemia, hypoglycemia, iron deficiency, hyperlipidemia, lack of energy and increased susceptibility of infections. The list is long, but the most of the complications are usually transient, easily manageable and limited [39, 40].

In a large Scandinavian retrospective study, 290 KD-fed children were investigated over two years follow up [41]. Side-effects were noted in 29 subjects and most of them were treatable. Only 4 patients needed to stop the therapy (due to hyperlipidaemia and to kidney-stones).

The relative effectiveness and tolerability of KD in ASD patients has been well documented in an online survey-based study that was conducted on large population (733 children with ASD and clinical seizures, subclinical epileptiform discharges or seizure-like activity and 290 controls) [42]. The questionnaire was validated and very detailed in documenting seizures and ASD core symptoms through parental reports while implementing anti-epileptic drug (AED) or non-AED treatment. Among non-antiepileptic drug (non-AED) treatments the KD was the third (after vitamin B6 and steroids) most commonly used intervention and, as compared with GFCF, was thought to decrease seizures significantly more. In addition, the survey provided an information about most common adverse effects regarding type of management. Ketogenic and Atkin's or modified Atkin's diet tended to result in drowsiness, tiredness, fatigue, constipation or diarrhea. 27% of responders declared one mild side effect that occurred during therapy with KD, 13% declared two and only 4% declared 3. Interestingly, AED treatments, except for ethosuximide, were reported to have a higher rate of adverse effects as compared to non-AED treatments, especially with respect to severe adverse effects.

## Summary

Although a number of clinical studies and reviews described KD as being relatively safe, this thera-

py requires careful complete physical and laboratory examination prior to the diet's initiation, and regular follow up visits. Moreover, to meet the specific medical needs of each patient an individualized dietary plan should be developed with caution by the patient's healthcare providers.

Based on the current scientific data, KD holds promise for ASD affected patients as an alternative treatment strategy. However, human studies in this field are scarce and establishing accurate recommendations for all ASD patients requires further large multicenter trials.

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The authors declare no conflict of interest.

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