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REVIEW ARTICLE

Are therapeutic diets an emerging additional choice in autism spectrum disorder management?

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Abstract

Background A nutritional background has been recognized in the pathophysiology of autism and a series of nutritional interventions have been considered as complementary therapeutic options. As available treatments and interventions are not effective in all individuals, new therapies could broaden management options for these patients. Our aim is to provide current literature data about the effect of therapeutic diets on autism spectrum disorder.

Data source A systematic review was conducted by two reviewers independently. Prospective clinical and preclinical studies were considered.

Result Therapeutic diets that have been used in children with autism include ketogenic and gluten/casein-free diet. We were able to identify 8 studies conducted in animal models of autism demonstrating a beneficial effect on neurophysiological and clinical parameters. Only 1 clinical study was found showing improvement in childhood autism rating scale after implementation of ketogenic diet. With regard to gluten/casein-free diet, 4 clinical studies were totally found with 2 of them showing a favorable outcome in children with autism. Furthermore, a combination of gluten-free and modified ketogenic diet in a study had a positive effect on social affect scores. No serious adverse events have been reported.

Conclusion Despite encouraging laboratory data, there is controversy about the real clinical effect of therapeutic diets in patients with autism. More research is needed to provide sounder scientific evidence.

Keywords Autism · Children · Gluten/casein-free diet · Ketogenic diet · Therapeutic diet

Introduction

Autism spectrum disorder is a group of developmental disabilities primarily characterized by impaired social interactions and repetitive and restricted behaviors. Although the contribution of genetic background to pathophysiology is indisputable, current research suggests that environmental modifiable factors can account for a large proportion of etiological variance [1]. According to gut-brain axis theory, early life nutritional programming (even during gestational or perinatal period) influences various aspects of cognitive function and may predispose to autism spectrum disorder occurrence [2, 3].

More specifically, it is now well established that the combined genetic composition of the intestinal microflora (intestinal microbiome) has been implicated in various ways with numerous aspects of human health. Experimental studies conducted in mouse models devoid of any microbiota have shown that gut microbiome has an impact on proper myelin formation as well as on microglia maturation and function. It is obvious that disturbance of the above procedures affects negatively brain connectivity patterns and immune response to infectious challenges [4]. Besides, by-products of the gut microbiota (e.g., lipopolysaccharides, short chain fatty acids) can alter gene transcription and modulate the profile of cytokines produced, while gut microbiota also influences synthesis of serotonin (via metabolism of tryptophan), a neuropeptide that is involved in the pathophysiology of autism spectrum disorder [5, 6]. In other words, altered microbiota composition may be an underlying factor contributing to the development of some of the traits of autism. On the

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other side, Central Nervous System disorders can modify gut permeability, motility and secretion (through the hypothalamus pituitary-adrenal axis, autonomic and neuroendocrine system) and consequently the microenvironment of the intestine, thus affecting microbiome composition, too [4]. Therefore, a bidirectional relationship and interaction exists between gut microbiome and central nervous system, which consists the basis of the so-called gutbrain axis.

Under this view, many researchers focus on assessment of nutritional status of children with autism spectrum disorder. There is evidence in the literature that these children exhibit selective eating patterns, gastrointestinal symptoms, nutrient deficiencies, as well as dysregulated metabolism. In a microscopic level significant differences in synthesis of intestinal microbiome have been observed between patients with autism and healthy controls. In this way, nutritional interventions should be considered as a potential alternative therapeutic approach of this population [7]. Furthermore, leaky gut syndrome in children with autism has been discussed by some researchers, as there are literature data (although limited) showing that patients with autism and their relatives exhibit increased permeability of the intestinal barrier in comparison to those without autism [8]. Indeed, the administration of specific nutrition supplements (fatty acids, vitamins/minerals) seems to have a beneficial effect on clinical parameters of a subset of patients [9]. It is also noteworthy that more than 80% of parents of children with autism report the use of some type of dietary intervention [10]. At the same time, specific diets seem to have their own place in the management of neurodevelopmental disorders [11]. On the other hand, there is still literature controversy about elimination or restrictive diets in terms of their flexibility, implementation criteria and adverse events [12].

Autism presents significant phenotypical variability and contributes to diversity within population, while these patients often have very special skills. However, autism is also associated with significant difficulties in everyday functioning and consequent financial burden for the families. For this reason, every therapeutic option resulting in alleviation of symptoms should be considered.

The aim of this review is to provide current data from preclinical and clinical studies about the effect of therapeutic diets on clinical as well as on neurophysiological aspects of autism.

Literature search

Eligibility criteria

Studies with the following criteria were selected: (1) prospective studies, (2) human studies conducted in children with diagnosis of autism spectrum disorder, (3) preclinical studies conducted in animal models of autism, (4) studies including measures of clinical or neurophysiological aspects of autism.

Search strategy and study selection

A comprehensive search was undertaken using Pubmed as the medical database source. The literature search and the eligibility assessment process were performed by two reviewers independently in all stages. No year-of-publication restriction was placed. The mesh terms that were used were: "therapeutic diet", "autism spectrum disorder", "autism", "ketogenic diet", "gluten-free diet", "gluten/casein-free diet".

After searching the literature, data were abstracted and selected articles were scanned to eliminate studies with irrelevant topic, methodological issues or duplicate records. Figure 1 illustrates the flow chart of how the articles were selected.

According to our results, two different types of therapeutic diets have been used in children with autism spectrum disorder until now: ketogenic and gluten/casein-free diet.

Basic principles of ketogenic diet

In general, ketogenic diet exerts a significant effect on brain energy metabolism. Ketogenic diet is based on high-fat, moderate-protein and low-carbohydrate components, thus resulting in limited metabolism of carbohydrates and proteins, enhanced fat metabolism and ketone bodies production. Ketone bodies are known to be a more efficient energy source than glucose, as they produce more ATP molecules per unit and, in this way, more energy is available for the brain. As ketone bodies are produced, they enter the cell through monocarboxylate transporters and induce ATP synthesis in mitochondria through Krebs cycle and oxidative

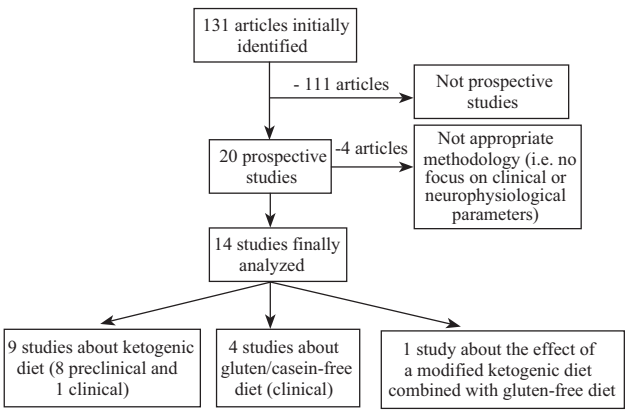

Fig. 1 Results of literature search about the effect of therapeutic diets in patients with autism spectrum disorder

phosphorylation, thus upregulating mitochondrial genes and promoting mitochondrial biogenesis, as assessed by electron microscopy [13, 14].

At the same time, a relationship between ketone bodies and neurotransmission is speculated. More specifically, studies have shown that acetoacetate and b-hydroxybutyric inhibit glutamate uptake into synaptic vesicles by vesicular glutamate transporters in pre-synaptic neurons, while acetoacetate may also inhibit glutamate release from hippocampal neurons. On the other side, mild acidosis in blood can inhibit pH-sensitive NMDA-type glutamate receptors, thus enhancing γ aminobutyric activity [13, 15, 16].

Ketogenic diet and autism

Potential mechanisms

In recent years, ketogenic diet has been used as a co-adjuvant and alternative therapeutic option in a variety of neurological disorders of childhood (e.g., brain tumors, mitochondriopathies, drug-resistant epilepsy) with varying outcomes. The hypothesis behind its use in children with autism spectrum disorder lies on a possible association of autistic phenotype with neurotransmission patterns, deficiencies in glucose metabolism, as well as mitochondrial dysfunction [17]. More specifically, studies performed with positron emission tomographic scans have demonstrated deficient glucose oxidation in these patients. On this basis, ketone bodies could be an alternative energy fuel in the central nervous system and improve brain function [18].

Neurobiological models also support a neurotransmitters' imbalance in the pathogenesis of autism. Increased levels of glutamate have been reported both in serum and in the cerebrospinal fluid of children with autism, while postmortem studies in individuals with autism have revealed amplified expression of genes associated with glutamergic pathways [19–22]. Besides, mitochondrial dysfunction is implicated in autism; a significant number of children with autism exhibit abnormal mitochondrial biomarkers (lactate, carnitine, pyruvate), while several genes known to regulate mitochondrial function have been proven to be autism-risk genes [23]. As ketogenic diet has been shown to increase γ aminobutyric acid against glutamate effect in central nervous system and also restore mitochondrial function, it could exert a beneficial role in individuals with autism spectrum disorder [13–16].

In summary, there are numerous hypotheses associating ketogenic diet with autism spectrum disorder. On the other hand, there are entities for which ketogenic diet consists a recognized therapeutic option (e.g., epilepsy, glucose transporter 1 and pyruvate dehydrogenase deficiencies). As these disorders can co-exist with autism, ketogenic diet could theoretically be an effective treatment for these children [24]. Literature data from preclinical and human studies evaluating its effect on autism spectrum disorder are available too.

Preclinical studies

Preclinical studies in animal models provide accumulating evidence for clinically beneficial effect of ketogenic diet in autism. We have identified in literature 8 experimental prospective studies investigating the effect of ketogenic diet on behavioral aspects and neurophysiological parameters of autism spectrum disorder [25–32]. The year-of-publication ranged from 2013 to 2017. Animal models used in these studies included: (i) BTBR mouse model (mice with a total absence of the corpus callosum and a severely reduced hippocampal commissure) in 3 studies, (ii) VPA rodent model (autism caused by prenatal exposure to valproate) in 2 studies, (iii) En2 mouse model (mice with alterations in Engrailed genes producing autism-related behaviors) in 1 study, (iv) EL mouse model (a natural model of autism and idiopathic epilepsy) in 1 study and (v) Long-Evans rats (the result of a cross between a female albino from the WISTAR Institute and a wild male captured near Berkeley and offspring selection mainly used in behavioral research) in 1 study, too.

According to results of these studies, the administration of ketogenic diet seems to improve social interactions, as shown by a variety of measures of sociability and also improves repetitive behaviors and increases nociceptive threshold. In none of the above studies, ketogenic diet worsened autistic phenotype. It is noteworthy that in some cases the beneficial effect is gender specific, as a less strict diet was equally effective in improving sociability and reducing repetitive behavior in female mice, but had limited effects in males [26]. Moreover, behavioral improvements are usually dissociable from any antiseizure effect. Table 1 summarizes main findings of the above studies.

The use of animal models also offers the opportunity to explore the underlying mechanism of these favorable effects. Autism is still lacking established biomarkers. However, histopathological changes, including altered neurogenesis, heterotopia, cortical dysplasia, have been described and genetic mutations associated with the development of autistic phenotype have been identified [33]. In this way, the impact of ketogenic diet on these histological or genetic "hallmarks" of autism could be investigated.

Indeed, Smith, et al. have shown that ketogenic diet can restore abnormal motor maps, low movement thresholds, as well as imbalances in excitation/inhibition ratio in animals' cortex [29]. In terms of neurotransmission, no significant changes in neurotransmitters' levels after ketogenic treatment have been detected, although Verpeut et al. have shown that exposure to ketogenic diet during the juvenile period increases specific neuronal populations in the cingulate

Table 1 Preclinical studies investigating the effect of ketogenic diet on animal models of autism

Authors	Year	Animal models	Outcome(s) studied	Duration of follow-up	Significant effect
Kasprowska-Liśkiewicz et al. [25]	2017	Long-Evans male rats	Sociability, locomotor activity, working memory, and anxiety-related behaviors	4 wk	Increased social exploration
Ruskin et al. [26]	2017	EL mice	Social contact time, repetitive behavior	4 wk	Improved social contact in females reduced repetitive behavior in males
Mychasiuk et al. [27]	2017	BTBR mice	Changes in mRNA and gene expression White matter development in temporal cortex/hippocampus	14 d	Modification in vitamin D receptor and steroid sensing receptor pregnane X pathway Improvement in white matter development
Verpeut et al. [28]	2016	En2 mice	Social outcomes	39 d	Improvement of social interaction and exploratory behavior
Smith et al. [29]	2016	BTBR mice	Brain motor maps, movement thresholds		Improvement of excitation/inhibition patterns
Castro et al. [30]	2016	Mice with valproate induced autism	Behavioral parameters		Improvement in sociability index and social novelty index
Ahn et al. [31]	2014	Prenatal valproate rodent model	Social behavior	10 d	Increase in the number of play initiations/attacks
Ruskin et al. [32]	2013	BTBR mice	Sociability, communication, repetitive behavior	3–5 wk	Enhance sociability Decrease self-directed behavior Increase communication of food preference

cortex, lateral septal nuclei, and anterior bed nucleus of the stria terminalis [28]. On the other side, Mychasiuk et al. suggest that ketogenic diet leads to changes in expression of genes associated with stress response, neuronal signaling and white matter development. This finding implies that after ketogenic treatment a reversal of genetic modifications negatively affecting neurodevelopment occurs [27].

Despite favorable and encouraging findings of preclinical studies, the generalizability of their conclusions should be speculated. Different animal models have been used in the aforementioned studies, thus leading to varying degrees of severity of autistic phenotype. Besides, the complexity of central nervous system physiology in humans may hinder the direct generalizability of experimental findings, while measures of clinical aspects (e.g., sociability) used in laboratory animals, as well as duration of interventions (usually days) are not applicable in children. Due to all these limitations, the need for clinical studies in humans is unavoidable.

Human studies

Data from clinical studies are generally few. We were able to identify only 1 prospective study investigating the effect of ketogenic diet on clinical aspects of autism (Table 2) [34]. In this study, ketogenic diet was applied to 30 children with autism for 6 months. Among children who complied with the diet (60% of participants) those with the milder autistic symptoms showed significant improvement in aspects like concentration, learning abilities or social behavior. Significant behavior was defined as an increase by > 12 units in Childhood Autism Rating Scale. The rest of participants showed mild to moderate improvement. It is also noteworthy that no clinical or biochemical evidence of inborn errors of metabolism was observed in any of the children who participated in the study. We have also identified in the literature a case report describing the administration of a gluten/casein-free modified ketogenic diet to a 12-year-old boy for

Table 2 Clinical prospective studies about the effect of ketogenic diet on clinical aspects of children with autism

Authors	Year	Sample	Outcome(s) studied	Duration of follow-up	Significant effect
Evangeliou et al. [34]	2003	30 children 4–10 y old	Childhood Autism Rating Scale	1 y	Significant improvement (> 12 units) in 2 patients & minor improvement (8–12 units) in 8 patients

14 months resulted in a remarkable improvement in seizure activity, cognitive and social skills, language function, as well as stereotypies [35]. However, beneficial effect in this patient cannot be solely attributed to ketogenic diet, as it was not the only dietary intervention applied. No serious adverse events were noticed in any of the above cases.

This lack in systematic clinical studies investigating the effect of ketogenic diet on children with autism could be attributed to potential complications. According to a recent retrospective study, adverse effects were observed in 80% of children after ketogenic diet initiation, with emesis, food refusal and hypoglycemia being the most frequent [36]. Additional early onset complications include hypertriglyceridemia, hyperuricemia, hepatitis, acute pancreatitis and persistent metabolic acidosis. Furthermore, the fact that ketogenic diet is a restrictive type of diet in terms of calculations and monitoring may exert a negative influence on final compliance of children and their families [36, 37].

Principles of gluten/casein-free diet

Gluten-free diet involves the strict exclusion of gluten, a mixture of proteins found in wheat and related grains, from a person's diet and has been traditionally implemented as the most effective treatment in patients with celiac disease [38]. It has also gained popularity in cases of non-celiac gluten sensitivity and wheat allergy. Nevertheless, barriers associated with its use and including low availability, cost, gluten cross-communication, as well as potential nutritional deficiency (esp. vitamins and minerals) should not be overlooked [39]. In some cases, the gluten-free diet is combined with a casein-free diet. Casein-free diet includes the removal from diet of casein (the main protein in dairy products) and has been classically considered in cases of galactosemia and in toddlers with cow milk allergy [40].

Gluten/casein-free diet and autism

Potential mechanisms

A number of theories have been proposed to explain the rationale for the use of this diet type (involving removal of both gluten and casein from a child's diet) in children with autism. Incomplete breakdown of gluten and casein can give genesis to a series of peptides, which may enter bloodstream, cross blood–brain barrier and finally interact with opioid receptors, thus altering neurotransmission patterns [40]. Indeed, there are emerging literature data showing that μ opioid receptors regulate the aspects of social behavior and may be involved in pathogenesis of autism spectrum disorder [41]. The entry of gluten- and casein-based peptides into systematic circulation is believed to be facilitated by increased intestinal permeability (the aforementioned "leaky gut hypothesis"), which is often reported in children with autism. This is also in accordance with the fact that children with autism spectrum disorder often present nonspecific gastrointestinal symptoms [40].

Furthermore, it is noteworthy that gluten sensitivity has been associated with additional neuropsychiatric entities, such as schizophrenia, ataxia or attention-deficit/hyperactivity disorder. According to Genuis et al., gluten exposure leads to the accumulation of toxicant burden, immune dysregulation and consequent release of proinflammatory cytokines. This proposed causative pathway could explain the multimorbidity often encountered in patients with gluten sensitivity [41].

Studies in literature

No preclinical studies on this topic have been identified. We were able to identify a total of 4 clinical prospective studies conducted in children with autism spectrum disorder [42–45]. In terms of study design 2 of them were double blind randomized controlled trials [42, 43], 1 of them was double blind crossover trial [44] and 1 was single blind study [45]. All of them compared gluten and casein-free diet versus normal diet. The gluten/casein-free diet or the conventional diet (placebo) was administered to participants through snacks indistinguishable from one another.

The year-of-publication ranged from 2002 to 2016. No studies investigating the effect of only gluten-free or only casein-free diet have been found. The number of participants in each study ranged from 10 to 72 children, the age of children recruited from 2 to 16 years, while the duration of the intervention ranged from 12 weeks to 12 months. Basic traits of the above studies are summarized in Table 3. In 2 of them evaluation of autistic traits was based on objective measures-scales [43, 45], in 1 study results were drawn from parents' diaries [42], while in 1 study researchers were based both on objective measures and on parental reports [44].

A significant beneficial effect of this type of diet on clinical aspects of autism was identified in 2 of the above studies (efficacy rate 50%) [43, 45]. It is noteworthy that in both of them the duration of the nutritional intervention was 12 months, while in the other 2 studies with no significant effect the total duration was 12 weeks. This finding implies that longer implementation of gluten/casein-free diet may be necessary to reveal changes in behavioral patterns of these children. Moreover, in trials without a significant effect authors were not based (only) on the evaluation of objective measures, but also on parental reports and this may introduce bias in the methodology [42, 44]. Data about adverse events are provided only in 1 study; they were characterized by authors as mild or moderate and mainly included constitutional problems (e.g., abdominal discomfort, diarrhea) and parent-reported insomnia and increase in problem behavior.

Table 3 Clinical prospective studies about the effect of gluten/casein-free diet on clinical aspects of children with autism

Authors	Year	Sample	Outcome(s) studied	Duration of follow-up	Significant effect
Hyman et al. [42]	2016	14 children with autism 3–5 y old	Physiologic functioning, behavior[a]	12 wk	No
Whiteley et al. [43]	2010	26 children with autism 4–11 y old	Autism Diagnostic Observation Schedule, Gilliam Autism Rating Scale, Vineland Adaptive Behavior Scales, Attention-Deficit Hyperactivity Disorder-IV Scale	12 mon	Yes (on specific subdomains of the scales used)
Elder et al. [44]	2006	15 children with autism 2–16 y old	Childhood Autism Rating Scale, Autism Diagnostic Interview—Revised, Ecological Communication Orientation Language Sampling Summary, in-home observation	12 wk	No
Knivsberg et al. [45]	2002	10 children with autism 5–10 y old	Movement Assessment Battery for Children, ITPA, Illinois Test of Psycholinguistic Abilities, Reynells spraktest, Leiter International Performance Scale	12 mon	Yes (on specific traits: attention, response to teaching, temper tantrums, linguistic skills, eye contact)

[a] Assessed by parental diaries

No nutritional deficiencies or excesses are reported [43]. Besides, in 2 studies authors report that children participated received dietary assessment by nutritionists and were given dietary supplements (iron, magnesium, calcium, vitamins) when needed [42, 43].

At this point, we should not omit to report a recent prospective study by Lee et al. which investigated the effect of a combination of gluten-free and modified ketogenic diet along with medium-chain triglycerides on children with autism spectrum disorder. Evaluation 3 months later revealed significant improvement in social affect score, but no difference was observed in restricted and repetitive behavior patterns. However, in this study the proportion of final adherence to diet was low (15 participants out of 27 who initially started the protocol) and no control group was included. Moreover, as a combination of dietary interventions was used, the isolated effect of gluten-free or ketogenic diet could not be estimated [46] (Table 4).

With regard to other types of studies about the effect of gluten/casein-free diet on autism, we were able to identify cross-sectional and retrospective studies in literature. According to Harris et al. no significant changes in scores on Gastrointestinal Symptoms Rating Scale and Childhood Autism Rating Scale were detected in children with autism before and after implementation of the diet, although parents report improved gastrointestinal and behavioral patterns [47]. Similarly, about one-third of parents report significant improvement on the autism spectrum disorder core symptoms in a recent retrospective study, while Pennesi et al. suggest that the presence of specific gastrointestinal symptoms in children with autism (e.g., food allergies) is associated with a better response in gluten/casein-free diet [48, 49]. On the same wavelength, Mari-Bauset et al. suggest that the use of gluten/casein-free diet should be restricted to children with autism spectrum disorder exhibiting a clear intolerance or allergy to foods containing the allergens excluded in this type of diet [50]. On the other side, it should be highlighted that an important barrier to evaluating benefits of treatment with gluten/casein-free diet for children with autism is the fact that gluten sensitivity usually has many "faces" and may be present in a variety of ways in these patients, including both neurologic and non-neurologic (e.g., gastrointestinal) signs and symptoms [51]. Due to this heterogeneity, there may be a difficulty in confirming clinical improvement in these children.

Comparison with other interventions-Future directions

Since both social and communication differences are part of the diagnosis, behavioral and speech therapy are considered to be the foundation of every intervention. There are

Table 4 Results of a study which investigated the effect of a combination of dietary interventions (modified ketogenic diet, gluten-free diet and medium-chain triglycerides) on children with autism spectrum disorder

Authors	Year	Sample	Outcome(s) studied	Duration of follow-up	Significant effect
Lee et al. [46]	2018	15 children with autism 2–20 y old	Autism Diagnostic Observation Schedule, 2nd edition Childhood Autism Rating Scale, 2nd edition	≥ 3 mon	Significant improvement only in social affect scores

no studies in the literature providing definite efficacy rates for these interventions. Nevertheless, in recent years there are research papers showing that some form of treatment is better than no treatment [52]. Most studies have been conducted about the effect of behavioral therapies, especially the method of applied behavior analysis. Differences in the structure of applied behavior analysis and the intensity of therapy do not affect the outcome [53, 54]. The main methodological drawbacks of the aforementioned studies are their small samples as well as the fact that they do not usually compare different treatment options and do not provide data about their relative effectiveness. Furthermore, each study focuses on a different aspect of autism spectrum disorder and this prevents from the generalizability of their conclusions.

Given the complexity of autism pathophysiology, it is evident that no single treatment or intervention can be effective in all individuals. Until now, scientific data about the real effect of therapeutic diets on autism are not sound enough to support a generalized use in all patients with autism spectrum disorder. Nevertheless, they could be used as a complementary treatment option in combination with traditional therapies (applied behavioral analysis, occupational therapy, ergotherapy, speech and language therapy, structured teaching, educational programs) to further alleviate some symptoms of autism and improve the aspects of everyday functioning. The challenge is to find specific traits (clinical or biochemical) of these patients which would predict benefit from dietary interventions so that the appropriate dietary intervention is implemented in the appropriate patient groups. This could be an interesting point of focus for future research [51].

In general, more randomized studies based on larger samples are needed to shed light in the above issues. Besides, from a methodological point of view it would be useful to define what we mean as an "improvement" in these children and to determine proper measures/scales which will be systematically used across studies. As autism presents significant phenotypical variability, there is a need to decide which aspects of this disorder are the most important and which symptoms are those whose alleviation would most improve everyday functioning. On the other side, the implementation of specific dietary interventions may raise difficulties for children and their families, including flexibility, resources, children's food preferences, and non-compliance [34]. Another challenge for future research is to investigate ways and methods for the best implementation of dietary changes without disturbing families' balance.

Conclusions

To the best of our knowledge, our work is the first review presenting both clinical and experimental data about the effect of therapeutic diets on autism spectrum disorder. Current literature knowledge provides evidence that ketogenic and casein/gluten-free diet may have their own place in our reserve for the therapeutic management of specific subsets of children with autism. Experimental preclinical studies support ketogenic diet as an additional choice in the management of autism and shed light into our understanding of metabolic-based therapies for neurological and developmental diseases. Nevertheless, clinical data from human studies about the effect of ketogenic diet are very few and in this way no safe recommendations can be made. On the other side, more clinical studies about the effect of gluten/casein-free diet in these patients are available. However, available data arise from studies with small sample size and are still controversial.

In general, despite encouraging data, no definite proof still exists. Under this view, the use of therapeutic diets in children with autism should be restricted to specific subgroups, such as children with autism and epilepsy or specific inborn errors of metabolism, children with known food intolerance/allergy or even children with food intolerance markers. Their implementation should always be guided by health care practitioners.

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Compliance with ethical standards

Ethical approval Not needed.

Conflicts of interest The authors declare that they have no conflict of interest.

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