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A Review of the Efficacy of the Dietary Intervention in Autism Spectrum Disorder

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Abstract

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BACKGROUND: Autism spectrum disorder (ASD) is an early-onset neurodevelopmental disorder with 1 in 68 children prevalence. The key symptoms of ASD include social deficits, verbal and non-verbal communication deficits, and restricted, repetitive patterns of behavior, interests, or activities. For unknown reasons, gastrointestinal symptoms are related to ASD. The aim of the current paper is to review the available literature on dietary interventions in children with ASD and provide up-to-date evidence.

METHODS: Searches in online databases, using the search terms 'dietary intervention,' 'autism spectrum disorders,' and 'autism' were conducted. The search targeted publications ranging from 2010 to 2020.

RESULTS: Twenty-six studies with different study designs which evaluated the effectiveness of specific dietary interventions in children with ASD were included in our review. Several dietary interventions were of popular practice in the management of children with ASD, including elimination (gluten-/casein-free diet and oligoantigenic diet), modification (modified ketogenic diet), supplementation (minerals, vitamins, omega 3, and omega 6), and exclusion (food additives). Studies showed different results with varying degrees of evidence. Overall, data were inadequate to make accurate conclusions.

CONCLUSION: There is little evidence to support the use of dietary interventions for children with ASD. Additional high-quality studies and further research are, therefore, needed.

Background

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that starts early in childhood and is characterized by impairment in reciprocal social communication and a tendency to engage in a repetitive, stereotyped pattern of behavior, interest, and activities [1]. The prevalence of ASD is increasing worldwide, with boys more affected than girls [2]. Recent studies estimated the prevalence of ASD to be 1 in 68 children, with as many as 50% of children showing behavioral regression around the age of three [3]. The etiological factors are heterogeneous and include genetic, epigenetic, and environmental factors; however, its pathogenesis remains unknown [1]. About 5%–15% of individuals with ASD have either a single gene disorder or chromosomal abnormality, and despite the link between ASD and some genetic disorders, for example, Fragile X syndrome and tuberous sclerosis, no specific gene has been identified [4]. Genetic factors are modulated by prenatal (e.g., exposed to antiepileptic drugs and advanced paternal age) [5], perinatal (e.g., infections during pregnancy and maternal autoimmune diseases) [6], and postnatal (e.g., prematurity and

obstetrical complications) [7] environmental factors in some patients.

It is apparent that, for unknown reasons, systemic clusters of symptoms are related to ASD, including gastrointestinal [GI] problems, mitochondrial dysfunction, and "allergic" symptoms, especially food intolerance and eczema [8]. Parents of children with ASD reported selective eating behavior in 58–67% of the cases [9].

With no known cure for ASD, most treatments have focused on improving the social, behavioral, and communicative symptoms. As a general principle, individuals with ASD require a comprehensive management approach that is individualized according to the child's age and specific needs. The variation and complexity of the presentation of children with ASD can lead to difficulties in determining the most effective interventions. At present, no medication treatments are approved for the core symptoms of ASD; however, some medications are approved by the Food Drug Administration for the associated irritability and aggression in children with ASD (i.e., risperidone and aripiprazole, [10]). A comprehensive multidisciplinary approach is recommended in the management of ASD in the practical clinical guidelines [11]. One of

the suggested elements of this approach is a dietary intervention, an available approach used with and without clinical supervision to alleviate GI and behavioral symptoms. Some authors have suggested that support for the nutritional and metabolic problems may be ameliorated by increasing nutrient intake, which may reduce the symptoms and comorbidities associated with ASD [12].

Accordingly, some therapists in clinical practice advise parents of children with ASD to follow certain dietary interventions, to improve some core or GI-related symptoms of ASD [13]. Several studies in the literature have investigated the effects of dietary interventions on ASD symptoms [14], [15], [16]. It would be beneficial for both clinicians and parents of children with ASD to receive evidence-based dietary interventions that address food preference and food selectivity in children with ASD.

The purpose of this paper is to provide up-to-date evidence for dietary interventions in children with ASD, including gluten-free and casein-free, ketogenic, and specific carbohydrate diets, as well as probiotics, polyunsaturated fatty acids, and dietary supplements (Vitamins A, C, B6, and B12; magnesium; and folate) by reviewing the available data. Focusing on medications is out of the scope of this paper.

Methodology

Methods

The researchers independently conducted a systematic search and review in two databases: PubMed and Google Scholar, using the search key terms “dietary intervention,” “autism spectrum disorders,” and “autism.” The reference lists of identified articles were also assessed to identify additional relevant articles. The search also included psychiatry textbooks and published and unpublished treatment guidelines. The targeted publications ranged from 2010 to 2020. A total of 26 articles were included and reviewed. The analyzed data were categorized into clinical and nutrition groups. Finally, the results were combined to ascertain information about the correlation between diet, dietary interventions, and ASD.

We developed inclusion criteria in consultation with an expert panel of clinicians, dietitians, and researchers. We included studies published in English of any design that examined relationships between diet, dietary interventions, and ASD.

The studies reviewed in this article used standardized criteria from DSM-IV, DSM-V, or ICD-10 (American Psychiatric Association 1994, 2013; World Health Organization 1993) to diagnose individuals with ASD.

Results

In some individuals with ASD, early diagnosis of nutritional deficiencies and metabolic disorders and implementing appropriate therapeutic interventions have significantly improved cognitive abilities and behavioral difficulties [17], [18], [19]. Despite the scarcity of sufficient scientific and clinical evidence that supports the role of dietary interventions as part of ASD management [20]; it is still commonly recommended as a part of ASD management by some health providers [21]. These dietary interventions are based on either addition or elimination of certain food elements and nutrients associated with GI symptoms in children with ASD, such as inflammatory bowel disease, food intolerance, and allergies. Children with ASD tend to have food selectivity in comparison to other kids without neurodevelopmental disorders. Factors that may affect food selectivity in children with ASD include GI problems and “allergic” symptoms, especially food intolerance and eczema. Other factors, as reviewed by Whiteley *et al.*, include food texture (69%), food appearance (58%), food taste (45%), smell (36%), and food temperature (22%) [22]. This food selectivity can result in nutritional imbalance which may eventually be detrimental on brain function [23]. Hence, the problem of food selectivity needs to be carefully addressed through appropriate dietary interventions.

Types of dietary interventions

In an effort to identify the role of dietary intervention in the management of ASD, researchers have investigated the GI tract (GIT)-related ASD symptoms. They found that protein digestive capacity may be impaired in some children with ASD, contributing to the abnormal immune activation and GI symptoms observed in these populations [24]. Studies have revealed decreased activity of several digestive enzymes as well as GI symptoms (loose stools and/or gaseousness), in children with ASD [25]. Other researchers have reported elevated levels of urinary peptides of dietary origin in children with ASD, providing further evidence that this population experiences impaired protein digestion, coupled with increased intestinal permeability [26]. Based on the results of the above-mentioned studies, researchers have found promising evidence to support the role of dietary interventions in children with ASD [24].

Gluten-free/Casein-free (GFCF) diets

Despite little evidence to support positive effects, GFCF diets are considered the most common types of dietary interventions used in ASD [27]. The focus on GFCF diets, as an important dietary approach for children with ASD, originates from the evidence of

comorbid GIT problems related to consumption of foods containing casein and gluten [28], [29]. However, the explanation for increased GI problems in ASD remains unclear. One possible explanation that received attention could be related to increased intestinal permeability, the so-called leaky gut [30], [31]. Based on the “opioid excess theory,” digestion of gluten and casein results in the production of peptides with an opioid activity that can enter the bloodstream when the gut permeability is high [32], [33]. Therefore, these neuroactive peptides would, in turn, bind to opioid receptors and are ultimately speculated to affect processes in the central nervous system [34].

The use of a gluten-free diet necessitates the examination of the effects of removing all the food items containing gluten (the protein found in starch foods such as wheat, oats, barley, or rye). This dietary intervention is based on the exclusion of these food items from the diet and replaced by special gluten-free food items. Another dietary approach used for individuals with ASD, is the gluten-free diet combined with a casein-free diet. Casein is a peptide commonly found in milk and other dairy products. Consequently, a casein-free diet involves eliminating the intake of milk and dairy products. The main idea is to follow this elimination for a certain period and then reintroduce the products containing gluten/casein gradually to examine its contribution to ASD symptoms [35]. Studies that evaluated gluten-/casein-free diets reported some improvements in communication and challenging behaviors; however, the evidence was inconclusive [36], [37], [38].

Modified ketogenic, gluten-free diet regimen

The ketogenic diet (KD) is a low-carbohydrate, moderate protein, high-fat diet that has emerged as a potential dietary intervention for ASD [39]. Some studies have supported the effectiveness of a modified ketogenic, gluten-free diet regimen with supplemental medium-chain triglyceride (MCT) as an effective dietary intervention for children with ASD. These studies support the notion that the KD alters neural cellular metabolism by utilizing ketone bodies as an alternative fuel for the brain [40].

Lee *et al.* reported moderate and substantial improvement in Autism Diagnostic Observation Scale-2 (approximately 20–50% improvement in the social affect domain) following the use of modified KD/GF/MCT for 3 months in children with ASD [39]. Accordingly, the authors have concluded that their results could support the suggestion that the KD components may offer an effective and safe treatment for children with ASD, especially for their social impairment. On the contrary, other researchers did not observe a significant correlation between beta-hydroxybutyrate “BHB” levels (a ketone synthesized in the liver from fatty acids when

the supply of glucose is too low for the body’s energetic needs, such as during periods of prolonged exercise, starvation, or absence of dietary sources) and the degree of improvement in ASD symptoms [41].

Role of vitamins and minerals in ASD

Some health-care professionals consider vitamins, mineral supplements, and other non-pharmacological interventions to play a role in improving some ASD symptoms. There is some evidence that vitamins and mineral supplementations support the body’s basic physiologic processes and impact various metabolic and nutritional abnormalities (e.g., sulfation, methylation, glutathione redox imbalances, oxidative stress, and mitochondrial dysfunction). Nevertheless, there is no substantial evidence to support the efficacy of vitamin and mineral supplementations in improving children with ASD symptoms [42]. A recent study investigated the effect of Vitamin A deficiency on children with ASD and concluded Vitamin A deficiency exacerbates the core symptoms in children with ASD, especially when there are comorbid GI symptoms [43]. Vitamin C may have an effect on children with ASD, based on its vital role in brain neurons development, functional maturation, and antioxidant effect [44].

Hatice *et al.* studied the relationship between Vitamin D and its receptors, homocysteine, Vitamins B6, B12, and folate levels in 60 children with ASD and 45 children as the control group. The study observed that the total score of the Childhood Autism Rating Scale was positively linked to low serum levels of Vitamins D, B6, B12, folate, and Vitamin D receptors and high homocysteine levels [45]. This implies that these nutrients may be involved in the etiopathogenesis of ASD [46]. These findings may be of fundamental importance to care providers of children with ASD.

ω -3 and ω -6 fatty acid supplementation

Researchers have also investigated the effect of supplementation with n–3 (ω -3) including docosahexaenoic acid and n–6 (ω -6) fatty acids including γ -linolenic acid on children born preterm who display early signs of ASD. They found that they helped promote cognitive development [47], [48]. They observed that children assigned to treatment with n–3 (ω -3) and n–6 (ω -6) fatty acids supplementation exhibited a significant reduction in ASD symptoms as per the Brief Infant-Toddler Social and Emotional Assessment scale, in comparison to the placebo group. However, the number of studies investigating the effectiveness of omega 3 supplements on alleviating the core symptoms of ASD was limited, and the overall effects were small, precluding definitive conclusions. Future large-scale randomized clinical trials are needed to confirm or refute the efficacy of omega 3 and 6 [49], [50].

Food additives exclusion diet

Feingold, an American pediatrician and allergist, was the first to suggest that allergy to food additives, such as artificial flavors and colors, as well as naturally occurring salicylates, could contribute to symptoms of neurodevelopmental disorders [51]. It is believed that people with ASD cannot tolerate a range of additives, including aspartame, monosodium glutamate, and artificial colors (e.g., sunset yellow {E110}, tartrazine {E102}, carmoisine {E122}, Ponceau 4R {E124}), and sodium benzoate {E211}), evidenced by adverse effects on their behavior. While the avoidance of particular additives is very common, there has been little good quality research on the effect of food additives on patients with ASD [52].

Oligoantigenic diet in ASD

Another dietary approach that has received considerable attention in children with ASD is the oligoantigenic diets. The basis for this diet is to mainly focus on eliminating suspected high allergenic food products rather than eliminating artificial colors, flavors, and preservatives precisely [35]. The oligoantigenic diet intervention, also known as the restricted elimination diet or hypoallergenic diet, follows a process that focuses on eliminating foods that are often highly allergenic, such as cow's milk, cheese, eggs, chocolate, and nuts. The oligoantigenic diet approach involves an elimination phase, typically 2–5 weeks, where specific food items would be completely excluded. The food items allowed in the elimination phase could consist of only a few hypoallergenic foods such as rice, turkey, lettuce, pears, and water [53]. The patient would then be monitored for a substantial decrease in ASD symptoms, which would indicate "food sensitivity." This would be followed by the reintroduction phase, which involves the introduction of specific food items and observation for triggering of symptoms. In total, the assessment period could take up to 18 months. Therefore, the elimination/reintroduction of diet serves as a "diagnostic" tool for identifying the specific food items responsible for the physical and/or behavioral disorders in children with ASD.

Jose *et al.* reviewed the most relevant available data for the dietary and nutritional interventions in children diagnosed with ASD. Table 1 summarizes the level of evidence to each dietary intervention that has been addressed in the current review.

acid supplementations, food additives, exclusion diet, and the oligoantigenic diet. Despite the variation in the results of the studies conducted on dietary interventions and supplements in children with ASD, the interventions long-term effects are not well addressed in the research. The Center for Disease Control and Prevention stresses that "while remedies that work for one child may not work for another, dietary changes or supplements are a worthwhile option to explore [55]." Many families of children with ASD use dietary interventions and supplements, even without clear evidence on safety and efficacy. Therefore, a comprehensive multidisciplinary team is required and should include families of autistic children in the management plan with particular advice on the risk and benefits of using dietary intervention and supplements. Child and adolescents' psychiatrists as well as other mental health-care professionals must receive training in nutritional principles for patients with ASD and other neurodevelopmental disorders.

Table 1: Levels of evidence of complementary and alternative treatments in children diagnosed with ASD*

Treatment	Evidence	Comments	Grade of evidence
Gluten-free diet/casein-free diet	Single-blind trials suggested a potential benefit in 5–7-year-old children with GI symptoms A double-blind trial does not show benefit	Need for studies to clarify the utility Risk of nutritional involvement Supervision by a specialist in nutrition	B
Omega-3 fatty acids	Several systematic reviews Studies report benefits but with many methodological problems	Absence of high-quality evidence that shows effectiveness on the core and associated symptoms ASD Need for more studies based on promising effects in other populations	C
Vitamins/minerals/supplements	A double-blind, placebo-controlled randomized trials	Significant methodological problems	C
Vitamin A	Theories	Significant possibility of harm	D
Vitamin C	No evidence of effectiveness Two double-blind, placebo-controlled trials	Some preliminary evidence Non-significant toxicity	B
Vitamin D	Circumstantial evidence-based treatment	Theories	D
Vitamins B6 and magnesium	2005 Cochrane review: No recommendation Update 2010: Same conclusion	Methodological problems Poor quality of the studies No recommendation Potential neurotoxicity of B6 and/or magnesium	D
Vitamin B12	A small open pilot study No additional studies since 2008 review Twelve-week double-blind, placebo-controlled study Improvement in a subgroup	Need for more studies to define responders' group	C+

A: More than 1 high-quality study with consistent results or an extensive multicenter study. B: A high-quality study or several studies with mild limitations. C: A study with important limitations. D: No evidence/theories/multiple studies with very serious limitations. *Adapted from Levy SE, Hyman SL [54]. ASD: Autism spectrum disorder.

Discussion

This review summarizes different dietary interventions for ASD, including gluten-free and casein-free, KDs, vitamins and minerals, omega 3 and 6 fatty

Conclusion

Despite many research efforts investigating the effects of dietary interventions in ASD, our review shows no consensus exists to support specific dietary

interventions and supplementations in this patient population. More high-quality, longitudinal studies are needed to investigate the effects of dietary interventions and supplements in children with ASD. Future guidelines should be more explicit concerning dietary interventions and supplementations for this complex and impairing condition.

Review Limitations

The number of studies investigating dietary interventions and supplementation in children with ASD is variable in their designs and results. ASD symptoms were not clearly described in some of these studies.

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