International Journal of Science and Healthcare Research
Vol. 9; Issue: 3; July-September 2024
Website: ijshr.com
Review Article *ISSN: 2455-7587*

Nutrition Approaches in Autism Spectrum Disorder

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DOI: https://doi.org/10.52403/ijshr.20240318

ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental problem of unknown etiology with an increasing prevalence. Genetic and environmental factors are known to be effective in ASD. Gastrointestinal system (GIS) problems are frequently observed. It is stated that GI problems may be a triggering factor for the abnormal behaviors seen in ASD. There are various nutritional approaches such as gluten-free-casein-free diet, ketogenic diet, Feingold diet to alleviate behavioral symptoms and GI problems seen in ASD. This review aimed to assess the effects of scientific evidence-based nutritional approaches on autism symptoms.

Keywords: autism spectrum disorder; ASD; eating patterns; food selectivity; nutrient intake

INTRODUCTION

Definition and history of autism spectrum disorder

Autism Spectrum Disorder (ASD) is a lifelong neurodevelopmental condition characterised by a range of deficits in social interaction and communication and repetitive patterns of conduct, interests or activities [1]. To describe the wide range of abilities and difficulties associated with ASD, the term "spectrum" is used. The use of the term "ASD" reflects the continuum of autism-related disorders and recognises the need to plan for assessment, diagnosis, intervention and support services for a greater number of individuals than previously recognized [2,3].

The term “autism” was first used in 1911 by Swiss psychiatrist Eugen Bleuler, who defined it as 'turning inward'. Bleuler used the term autistic for individuals who completely isolated themselves from the outside world [3].

Leo Kanner and Hans Asperger first published studies on autism in 1943 and 1944. Kanner described 11 cases of early childhood autism, in which delays in language and cognitive abilities were observed. Asperger described 4 children with what he called “autistic psychopathy”, who had above average intelligence, psychomotor instability, bizarre interests and well-developed speech. The children in Kenner's group were generally more severely retarded and had limited communication. However, both authors distinguish autism from schizophrenia [4-6].

Dr. Kanner's and Dr. Asperger's observations are still valid today. They helped shape the current definition of how Autism is defined. However, autism was not immediately recognized as a separate diagnostic category by the American Psychiatric Association (APA) and the World Health Organization (WHO). For a long time, autism was confused with psychosis and schizophrenia. The APA did not publish separate criteria for autism until 1980, when the Diagnostic and Statistical Manual of Mental Disorders, First Edition (DSM-I) defined autism as a “psychotic reaction” and associated it with childhood schizophrenia. In DSM-II, “autistic behavior” was included in the definition of childhood schizophrenia. In the

International Classification of Diseases, Eighth Revision (ICD-8), autism was listed under schizophrenia as "infantile autism" [7,8]. In DSM-III in 1980, "infantile autism" was separated from schizophrenia and included in the category of "pervasive developmental disorder (PDD)". The term "autistic disorder" was included in DSM-III-R in 1987. In ICD-9, "infantile autism" was defined under psychoses of childhood-specific origin [8-10].

The diagnostic criteria for autistic disorders were clarified by the APA in DSM-IV in 1994. A similar classification was proposed in ICD-10 in 1993. DSM-IV classifies autism as a PDD along with 'Asperger's', 'Disintegrative Disorder', 'Rett's' and 'PDD-Not Otherwise Specified'[11,12]. The term "autism spectrum disorder" was first used as a synonym for PDD in the DSM-IV-TR revision. In the DSM-IV-TR, three criteria were defined for the diagnosis of autistic disorder: communication disorder, social deficits and repetitive behaviors with limited interests [4].

In 2013, in DSM-V, the overarching term PDD was replaced by ASD, which was also recommended for ICD-11. In DSM-V, the three domains of DSM-IV-TR were reduced to two: social communication and limited interest/repetitive behaviors. PDD disorders other than Rett syndrome are grouped under a single diagnosis called ASD. This term is used to refer to ASD on a continuum ranging from mild to severe. Instead of diagnostic subtypes, signs indicating the severity level of ASD symptoms along with intellectual and/or language impairment were given[7,8,13,14].

DSM-V-TR, published 2022, made no overall changes but revised diagnostic criteria for persistent social communication and interaction deficits. The DSM-V-TR stipulates that the presence of all symptoms pertaining to social communication difficulties is requisite for a diagnosis of ASD (15,16).

Epidemiology of Autism

Over the past 20 years, the prevalence of ASD, originally defined as a rare childhood disorder, has rapidly increased worldwide. This rise is due to greater recognition, broadening of diagnostic criteria, improved diagnostic tools and reporting [17]. In addition, some studies have attributed this increase to prenatal or postnatal exposure of the mother to environmental pollutants, tobacco and alcohol [18,19].

Countries vary in the prevalence of ASD. These differences may be due to the influence of biological or social factors (including gender, socioeconomic status, and ethnicity) on the prevalence of ASD [20]. Considering the global prevalence, it has been reported that 1 in every 100 children is diagnosed with autism [21]. In a systematic review conducted by Salari and colleagues, the global prevalence of ASD was determined to be 0.6%. In subgroup analyses, the prevalence of ASD has been documented at 0.4% in Asia, 1% in America, 0.5% in Europe, 1% in Africa, and 1.7% in Australia. The prevalence showed large differences within and between sociodemographic groups [17]. In 2000, the Centers for Disease Control and Prevention (CDC) started to monitor the prevalence of ASD in children in the USA. While the first reports showed that 1 in every 150 children was diagnosed with autism, 1 in every 36 children was diagnosed with autism in 2020[22].

Men are three to four times more likely to have ASD than women. Although it is common in men, it is thought to be more severe and associated with intellectual disability in women. In addition, women may be diagnosed with ASD later or not at all than men[23].

Autism development and diagnostic criteria

Impaired social interaction, verbal and nonverbal communication deficits, and the occurrence of restricted and repetitive behaviors are diagnostic features of ASD. The symptoms are usually recognized before the age of three years, usually in the

second year of life (12 to 24 months). Children with more severe developmental delays may be diagnosed earlier, while those with milder developmental delays may be diagnosed later [13,24,25].

The first symptoms of ASD are usually social apathy, unusual social interactions, bizarre play patterns and delayed language development. In subsequent years, bizarre and repetitive patterns of behavior and the absence of typical play become more prominent. Distinguishing between a diagnosis of ASD and restricted and repetitive behaviors can be difficult in preschool children, as most developing young children have strong preferences and enjoy repetition. The clinical distinction is based on the type, frequency and intensity of the behavior[13,24].

ASD is diagnosed when certain symptoms are found. A reliable diagnosis can be made based on a developmental history focusing on social skills and behaviors. ASD is common but there are no clear biomarkers. The APA's DSM-V-TR criteria are used to diagnose ASD. The DSM-V has been used as a global diagnostic tool for ASD since 2013[3,25].

The DSM-V-TR requires deficits in all three social domains in category A for a person to be diagnosed with ASD. Meet criteria A, B, C and D, currently or in the past[13,15].

A) The persistent inadequacy of social communication and social interaction, now or in the past in different forms.
   1) Inadequate social-emotional responsiveness
   2) Inadequacies in non-verbal communicative behaviors used for social interaction
   3) Difficulty developing, maintaining and understanding relationships
B) Limited, repetitive behaviors, interests or affects, present or past, manifested by the presence of at least two of the following.
   1) Stereotyped or repetitive motor movements, object use, or speech
   2) Persistence, strict adherence to routines or ritualized verbal or non-verbal behaviors,
   3) Limited fixed interests that are unusual in subject matter or intensity
   4) Sensory over- or under-sensitivity or excessive interest in the sensory dimension of stimuli
C) Symptoms must have been present early in development (they may not have been recognized until they crossed the boundaries of societal expectations or may have been overshadowed by ways they learned later).
D) Symptoms should lead to clinically significant impairment in social, occupational or other important areas.

The DSM-5 also recognizes that early symptoms may occur or that autism symptoms may not be recognized until later in life, even in people who are observed early in life.

Etiology of Autism

The etiology of ASD remains incompletely understood. However, the high prevalence of medical disorders in individuals with this syndrome provides compelling evidence for a biological etiology. Genetic factors can explain only 10-20% of ASD cases, while environmental factors play an important role. Prenatal and perinatal environmental exposures, maternal metabolic status, diet, diabetes, stress, drugs and lifestyle may increase the risk of neuropsychiatric disorders in children [26,27]. Research on potential etiologic mechanisms in ASD is ongoing, but there is currently no single unifying mechanism.

Research on twins and families has shown that genetics plays a role in autism. A meta-analysis conducted in 2016 showed that the majority (74-93%) of ASD risk is hereditary. However, this analysis also emphasized the important role of non-genetic factors [28]. The estimated risk of relapse among siblings of autistic children ranges from 3% to 18%, and this prevalence

increases as the number of siblings diagnosed with ASD increases[29,30].

The idea of genetic risk has changed in recent years. Many different genetic variants have now been linked to ASD risk. The genetic causes of ASD are very different and are thought to result from different forms of genetic variation. Evidence for genetic links to ASD comes from genes linked to learning disabilities or mental illness, genes involved in similar pathways, genes that raise ASD risk, genes affected by rare or common changes in DNA, and environmental factors that affect genes [31,32]. There are thought to be more than 800 genes identified as potentially associated with autism. These genes encode proteins related to chromatin remodeling, transcriptional regulation, cellular proliferation and especially synaptic architecture and function [33]. About 20% of ASD cases are caused by rare genetic factors linked to ASD-related syndromes (e.g. Fragile X syndrome), chromosomal abnormalities, and specific genes [31]. However, despite extensive research, the genetic etiology of at least 70% of ASD cases remains unresolved [34].

Abnormalities in the genetic code can lead to structural and functional abnormalities in the brain during brain development, to cognitive and neurobiological problems, and to symptomatic behaviors. ASD is no longer thought of as a disorder that is limited to a single area of the brain. Instead, it is recognized as general brain reorganization that begins early in development [24]. Available research on what causes autism suggests that there may be an association between autism and disorders that affect brain structure and function. Brain volume increases significantly during infancy and early childhood, according to available evidence. The brains of children with ASD may develop faster than usual, which can lead to different connections [35,36]. Results suggest that besides an overall underconnectivity of the brain, there is local overconnectivity, most commonly in the frontal and occipital regions [37,38].

Sibling studies show that the environment is as important as genes in autism[29,39]. Although there is evidence that ASD is strongly inherited, genetic factors alone are not enough; environmental factors are important as well. ASD is a complex disorder with many contributing factors, although it has a strong genetic component. Potential environmental causes include exposure to viruses, immune system abnormalities, vaccines, birth-related factors, bacterial infections, exposure to toxins and familial causes. Autism may be related to prenatal and postnatal factors, especially late birth (>40 weeks) [40-42].

Comorbid Conditions in ASD

Although intellectual disability is the most common comorbidity with ASD, it shows comorbidity with many psychiatric diseases. Some other medical disorders, like epilepsy and cerebral palsy, also occur in ASD [7,32].

The disorders that most commonly accompany ASD are [32]:

- Psychiatric disorders (such as attention deficit, bipolar, depressive and obsessive-compulsive disorders)
- Hyperlexia
- Sleep Disorders
- Eating disorders
- Nutrition Disorders
- Gastrointestinal system (GIS) problems and Obesity
- Other medical disorders (epilepsy, cerebral palsy)

Medical comorbidities are substantially more common in children with ASD and they often have medical conditions that affect more than one system. GIS dysfunction is among the most commonly reported comorbidities [43].

Treatment Approaches for ASD

To date, no treatment for ASD has been demonstrated to be both effective and specific. Treatment is aimed at improving functioning, identifying deficits and improving quality of life in ASD. Early intervention helps children communicate, walk, and interact with others. Treatment

approaches for ASD include behavioral and communication techniques, dietary interventions, pharmacological agents, and complementary and alternative approaches [44,45].

While there are no medications that directly affect the main symptoms of ASD, medications are often used for accompanying behavioral problems and comorbid psychiatric diagnoses. It is not uncommon for families of children with autism to express concern about the potential adverse effects of medications and to seek alternative, safer treatments. Biological alternative therapies often include dietary interventions, vitamin supplements and herbal medicines [46]. Some herbal treatments, such as Gingko biloba, Zingiber officinale (ginger), Astralagus Membranecaeus, Centella asiatica (gotu cola), and Acorus Calamus (calamus), may provide therapeutic benefits due to their somatic effects, such as increased cerebral circulation, increased cognitive function, calming or sedative effects, and increased immune response [47].

There are numerous factors that may impede a child with ASD from attaining the essential nutrition for optimal growth and development. Some children with autism prefer certain foods based on the sensory experience the food creates in their mouths. Other children may avoid certain foods because of stomach distress or discomfort. In addition, some children follow restrictive diets to alleviate the symptoms of autism [48]. A systematic review showed that 75% of individuals with ASD preferred special diets or dietary supplements as an alternative treatment option. This is regarded as indicative of the prevalence of the use of complementary and alternative medicine in ASD [49].

Nutritional problems accompanying ASD

Ensuring adequate nutritional intake is an important challenge in children with ASD. Approximately 90% of children with ASD experience anxiety related to feeding [50]. GIS problems, like constipation, diarrhea, and steatorrhea, as well as food allergies, metabolic disorders, and eating disorders, can make it hard for children with ASD to get the nutrients they need. The use of multivitamin and mineral supplements has been linked to an alleviation of autism symptoms, potentially due to their capacity to address GIS issues commonly associated with autism [43,51].

Gastrointestinal System Problems

Leo Kanner, in his article describing autism, stated that 6 out of 10 children with autism experience “severe feeding difficulties from the beginning of life.” Many studies have looked at the link between ASD, GIS symptoms and nutrition. The idea that individuals with ASD have unhealthy bowels stems from the markedly increased prevalence of GIS symptoms [52].

GIS disorders are among the problems that often accompany autism in children. A meta-analysis has shown that GIS complaints in children with ASD are associated with an increased risk of constipation, diarrhea abdominal pain. GIS issues are prevalent among children with ASD. They occur in 46% to 85% of children with ASD. It has been established that children with autism are more prone to experience difficulties with feeding. This can cause GIS difficulties. Food selectivity (FS) is associated with malnutrition, altered intestinal motility and constipation in people with ASD [43,53,54]. In a study conducted in China, 53 children with ASD exhibited many abnormalities in eating behavior and gastrointestinal symptoms compared to typically developing children [55].

The presence of FS in children with ASD has been linked to an elevated incidence of GIS symptoms, including constipation and diarrhea. These children like foods high in simple carbohydrates like sugary foods, but they don't like vegetables and fruit with a lot of fiber, which can cause problems. Nutritional interventions may improve overall symptoms [43,56]. In a study of 176 children in the USA, at least one GIS symptom was reported in the majority of

children (93.2%). Furthermore, severity of GIS symptoms was associated with repetitive behaviors [57].

It is crucial to comprehend the prevalence of GIS symptoms in individuals with ASD and their correlation with other behavioral domains that impact the child's quality of life. This understanding is important for identifying potential therapeutic interventions. Nevertheless, there is a dearth of guidelines that align with current practices for children with autism. A group of nutritionists should be formed to create a guide for treating children with autism [57,58].

The role of the gut as a potential contributor to the development of ASD is a rapidly evolving field of scientific inquiry. It is postulated that the gut microbiota and its metabolic products may be involved in the pathogenesis of ASD. The gut-brain axis represents a communication pathway between the GIS and the central nervous system. There is growing evidence that this pathway may be a contributing factor to the development of autism. The gut microbiota affects brain function through several ways, including neuroendocrine, neuroimmune and autonomic nervous systems, and toxin production. Increased intestinal permeability in individuals with ASD is seen as part of a condition called “leaky gut”. The “Leaky Gut Hypothesis” refers to a disruption in the epithelial barrier function of the small and large intestine. The disturbance of the blood-brain barrier permits the passage of a variety of metabolites. Tight junctions in intestinal cells are important for the intestine's barrier function. The heightened intestinal permeability evident in subjects with ASD indicates a possible involvement of the gut-brain axis in the underlying mechanisms of this condition [59,60]. A study in mice supported that a “leaky gut” mediated by lipopolysaccharide may be a trigger for the development of autism [61].

The composition of the gut microbiota in children diagnosed with ASD is less diverse in comparison to that of children who have not been diagnosed with ASD. Furthermore, the levels of Bifidobacterium and Firmicutes are generally lower, while those of Lactobacillus, Clostridium, Bacteroidetes, and Sarcina are higher. The Clostridium histolyticum group (Clostridium cluster II and I) has been observed to have a higher prevalence in the fecal matter of children with ASD. These bacteria can produce neurotoxins and have systemic effects. This emphasizes the importance of reducing Clostridium to bring about improvements in children with ASD. There are also changes in the levels of Bifidobacterium, Prevotella and Sutterella in children with ASD [59]. A study of individuals with severe ASD revealed an elevated ratio of Firmicutes to Bacteroidetes. This is thought to be because there are fewer Bacteroidetes [62]. A different study showed that autistic children have more Clostridium and enterococcus in their stool than children without autism. Autistic children also had more Firmicutes and fewer Bacteroidetes [63].

The fermentation products of carbohydrates in the colon are called short-chain fatty acids (SCFAs). They have been demonstrated to affect energy homeostasis, body weight, and colon cancer risk. SCFAs, especially propionate, affect the nervous system in children with ASD. This can cause developmental delays or seizures. Studies on animals have shown that propionate can affect the brain in ways similar to autism and cause autism-like behaviors. Children with ASD have more SCFAs and SCFA-producing bacteria in their stools. The fecal samples of children with ASD exhibited a higher concentration of SCFAs and bacteria capable of producing SCFAs [59,64].

A systemic review shows that certain probiotics and diets may be effective in rebuilding healthy gut microbiota and improving gut health [65]. Probiotics can strengthen the gut barrier, protect against gut pathogens, increase digestive enzymes and regulate immune responses. These effects may help treat ASD by affecting the gut-brain connection. Research suggests that probiotic administration may improve

gastrointestinal symptoms, microbiota and inflammation in individuals with ASD and alleviate autism symptoms [58,66]. Probiotic supplements have been found to increase Bifidobacteria and Lactobacilli levels, reduce body weight and provide overall improvement. The findings indicated that probiotics exert a beneficial influence on both behavioral and GIS symptoms of ASD[67]. A pilot study in 2019 also supported these findings [68].

Eating Disorders in ASD

Children with ASD often have difficulty eating. Most children develop eating disorders by age two, but children with ASD often face these disorders more severely for life. These disorders are characterized by symptoms such as selective food consumption, underconsumption of certain food groups, food sensory problems, decreased appetite, challenging mealtime behaviors and food neophobia [69-71].

Although FS and sensitivity are considered developmentally normal behaviors in young children, they are more common in children with autism. FS is often characterized by avoidance of certain foods, limited food variety and increased consumption of certain foods. These children often exhibit feeding habits based on specific temperature, color, shape or brand. This suggests that taste, smell and texture play important sensory roles in food acceptance or rejection. Being picky in children with ASD can make their diet even more restrictive. A significant proportion of parents of children with ASD indicate that their child has a limited food repertoire, which may increase the risk of malnutrition [72,73]. In a study conducted by Rodrigues and colleagues, children with ASD were found to have a higher incidence of FS than typically developing children [72]. A study conducted in Italy supported the relationship between FS and sensory areas [74]. These results supported the relationship between FS and sensory hypersensitivity in a longitudinal study with children with ASD [75]. Bandini et al. reported that FS may continue from childhood to adolescence, but they did not observe a significant increase in food repertoire. They emphasized the need for interventions in early childhood to increase diversity and promote healthy eating among children with ASD [76]. Schreck et al. found that children with autism had a smaller food choice and more nutritional problems than children without autism [77]. Children with ASD are less comfortable trying new foods than children without ASD. Children with ASD had higher rates of food avoidance associated with lower BMI [78].

Nutritional deficiencies are more likely in children with restricted diets. This highlights the need to establish specific criteria to define the severity and extent of FS in children with ASD. Individuals with ASD who have FS often reject vegetables, which can lead to nutrient deficiencies. These individuals often consume foods that are low in fiber, high in saturated fat and simple carbohydrates. Furthermore, it should be emphasized that children with ASD-FS prefer highly processed and calorie-dense foods and the effects of these foods on nutrition and gastrointestinal health [69,79,80].

Body Weight Gain and Obesity in ASD

Children with ASD may have higher rates of obesity and overweight compared to children without ASD. This higher risk of obesity may be due to eating behaviors, lifestyle (such as lack of physical activity), secondary comorbidities and medication use. In addition, reduced diversity of gut microbiota, hormonal imbalances and maternal metabolic disorders may also have an impact [81].

Children with ASD often refuse fruits, vegetables or proteins, and prefer starches, snacks and processed foods. An increased risk of excessive weight gain has been associated with increased consumption of snacks and high-calorie foods. Risk factors associated with ASD and obesity may differ significantly between individuals and cannot be applied to all children with ASD [56,64].

A meta-analysis has confirmed that obesity is highly prevalent in children with ASD, emphasizing the importance of this relationship. Preventing a decline in quality of life can be achieved by reducing obesity [82,83]. Studies have shown that obesity rates are higher in children with ASD than in healthy children. These individuals are at risk for obesity [84,85]. A study conducted in the USA demonstrated a markedly high prevalence of both overweight and obesity among adults diagnosed with ASD. These findings point to prevention of excessive weight gain as an important intervention target, especially in individuals with ASD with severe symptoms [86].

Nutrient Deficiencies in ASD

Although the nutrient requirements of children with ASD are similar to healthy children, FS, gastrointestinal problems and dietary habits can reduce micronutrient intake and lead to deficiencies. This can lead to worsening of autistic symptoms. Studies have shown that micronutrient intake is often low in children with ASD [27,56]. For example, children with ASD may have lower intakes of nutrients such as magnesium, selenium, vitamins A, D, and E, folic acid, and iron [87]. A study carried out in the USA revealed that children with ASD displayed markedly lower levels of energy intake, along with significantly reduced consumption of vitamins A and C, and zinc, within the 4-8 age cohort. Conversely, within the 9-11 age range, their intake of phosphorus was found to be below the recommended levels. In both groups, only a small proportion of children met the recommended intake levels for fiber, choline, calcium, vitamin D, vitamin K, and potassium [88]. A study by Figuerola et al. revealed that children with ASD consumed less protein, calcium, phosphorus, selenium, vitamin D, thiamine, riboflavin, and vitamin B12 than control subjects. Conversely, these children consumed more polyunsaturated fatty acids and vitamin E [89]. A study conducted by Malhi and colleagues demonstrated that children with ASD exhibited reduced consumption of fruits, vegetables, and protein, in addition to lower intakes of potassium, protein, vitamin C, thiamine, and folate [90]. The findings of a case-control study indicated that children with ASD had insufficient intakes of certain vitamins and minerals, including B vitamins such as B_1, B_2, B_3, B_6, and folate, as well as calcium. These deficiencies may be associated with selective or problematic eating behaviors leading to restriction of food intake in children with ASD [91].

Due to feeding difficulties, parents often turn to nutritional supplements to improve their child's nutritional status. Multivitamins and minerals are the most common supplements, but they may not have enough micronutrients (like choline and potassium) that many children with ASD lack. The most common problems are vitamin, mineral, and fatty acid deficiencies. For example, levels of pantothenic acid, folate, biotin, vitamin B_{12}, vitamin D, and vitamin E are often low. Deficiencies in metabolic processes such as cellular methylation and glutathione-mediated antioxidant defense have also been found. Therefore, it is thought that vitamin B_{12} may increase methylation and antioxidant capacity. Antioxidants like vitamins C and E are popular because of increased oxidative stress [27,92].

The objective of a systematic review was to evaluate the effects of various nutritional supplements, including amino acids, fatty acids and vitamins/minerals. According to this review, the efficacy of pyridoxine-magnesium supplements is controversial, while no significant effects were found for fatty acids and inositol. Some encouraging results were obtained for ascorbic acid and methyl B_{12} supplements and no serious side effects were reported in most individuals receiving supplements [93]. In a study conducted by Feng et al., the effect of vitamin D_3 supplementation was analyzed in a cohort of 215 children with ASD and 285 healthy controls. The study demonstrated that children with ASD exhibited serum 25-hydroxyvitamin D (25(OH)D) levels that

were significantly lower compared to healthy control subjects. Following vitamin D_3 supplementation, a notable decline in symptom scores was observed. The data indicated that treatment outcomes were more evident in young children with ASD, and emphasized the potential involvement of vitamin D deficiency in the etiology of ASD. Vitamin D_3 supplementation demonstrated promise in improving outcomes [94].

Although there is currently no compelling evidence regarding the levels of omega-3 (n-3) fatty acids present in children diagnosed with ASD, research has indicated an elevated n-6/n-3 ratio. High levels of n-6/n-3 in individuals with ASD can cause inflammation. It has been proposed that a lack of n-3 fatty acids may be associated with autism symptoms, and that supplementation may have a beneficial effect on these symptoms [27,92]. Recent research indicates that n-3 supplementation may offer a potential improvement in certain symptoms associated with ASD [95,96].

Studies found no significant difference in macronutrient intake between children with ASD and healthy children. Children with ASD who choose more selective diets are at risk of lacking nutrients [97].

Nutrition Approaches in ASD

Some diets, such as antioxidant diets, gluten-free/casein-free diets, or ketogenic diets, may result in the alleviation of ASD-related symptoms. However, other diets have not shown behavioral differences compared to control diets or have been linked to unfavorable outcomes, such as inadequate or excessive food intake. Other dietary interventions such as elimination diets, diets without food additives or specific carbohydrate diets may have led to some improvements, but it is unclear whether these diets can be therapeutically supported. There are diet guidelines for children with ASD who have GIS. These children need special attention to FS and general nutrition. A child with constipation needs to eat the right types of fruit, veg and whole grains. Appropriate interventions require a comprehensive dietary assessment and individualized recommendations by a trained dietitian. More research is needed on diet-related therapeutic solutions for ASD [64].

Gluten Free/Casein Free Diet (GFCF)

GFCF diets are one of the popular interventions for children with ASD and are often associated with GIS problems. The rationale for these diets is related to the systematic circulation of gluten and casein-based peptides with increased intestinal permeability, which is often seen in children with autism. This supports a theory called the “leaky gut hypothesis”. The theory is that gluten and casein produce opioid-like peptides when digested. These can enter the bloodstream when the gut is leaky. Under normal conditions, the GIS enzymatically breaks down the peptides of proteins; however, when this breakdown is incomplete, opioid peptides are formed. Opioids are chemical compounds that affect the brain and nervous system. Neuroactive peptides affect central nervous system processes by binding to opioid receptors. Therefore, changes in autistic behaviors can be observed by eliminating these substances from the diet. Gluten-free diets eliminate gluten-containing grains such as wheat, oats, barley and rye from the diet. Thus, gluten-containing products are replaced with gluten-free alternatives. Sometimes, people on a gluten-free diet avoid casein as well. Casein-free diets eliminate milk and dairy products. GFCF dietary practices require significant changes in children's eating routines, which may affect their eating behaviors and complicate their social integration [98-101].

A study involving 80 children, over half of whom had GI issues, demonstrated that a gluten-free diet led to notable improvements in GI symptoms and behavioral changes [102]. A study compared 20 children with autism on a GFCF diet with 85 children on a normal diet. The children on the GFCF diet

had higher energy, calcium, phosphorus, and sodium intake, but lower fiber, legume, and vegetable intake. In addition, while this group consumed higher quality fats, they needed to take vitamin D supplements [99].

GFCF can lead to reduced diversity of gut bacteria, increased opportunistic pathogens and immunosuppression. It is possible that GFCF may have a negative impact on the elasticity and stability of the gut, which could subsequently affect the gut microbiota. Furthermore, this diet restricts fiber from cereal products and may lead to chronic constipation [58]. A systemic review recommends using this diet only after a diagnosis of tolerance or allergy to foods containing allergens excluded from the GCFC diet [103].

Ketogenic Diet (KD)

A reduction in carbohydrate intake and an increase in protein consumption results in the production of ketone bodies (acetoacetate, β-hydroxybutyrate, acetone) in the liver. The ketogenic diet (KD), which forces the body to use ketones as fuel, has been recommended for its beneficial effects on metabolic and epileptic seizures. Using ketones as fuel can reduce symptoms. However, KD can have side effects such as constipation, high serum cholesterol, low serum protein, hemolytic anemia, menstrual irregularities, vomiting and dehydration. CD effects on ASD need to be understood before using it to treat ASD [104].

In a case-control study on children with ASD, El-Rashidy et al. divided the children into three groups: control, modified Atkins (ketogenic) diet and GFCF diet. The study found that both diets had positive results. The ketogenic diet group showed better development in terms of cognition and social skills [105].

Spesific Carbonhydrate Diet (SCD)

The Special Carbohydrate Diet (SCD) is a nutritional approach developed in the 1930s. It restricts complex carbohydrates and completely eliminates simple carbohydrates, taking into account malabsorption of both simple and complex carbohydrates. SCD is believed to have beneficial effects in the treatment of various diseases, including irritable bowel syndrome, celiac disease, and ASD [106].

The aim of SCD is to control damaged intestinal walls and overgrowing bacteria, to restrict the types of carbohydrates that intestinal pathogens feed on, and thus to restore the intestinal flora. It also encourages the use of fermented foods, especially homemade yogurts and probiotics. The SCD diet is very similar to the Paleolithic diet, except that it allows the consumption of some legumes, fermented dairy products and dry alcohol. It prohibits starch and includes mainly meat, chicken, fish, eggs, vegetables, fresh fruit, nuts and oilseeds. The diet starts with limited food intake and is gradually increased as the intestinal tract recovers [107].

Feingold Diet

Phenol is a naturally occurring organic compound that features an aromatic benzene ring. It is commonly found in salicylates and is also manufactured through chemical processes for use in artificial food additives. Phenols can be artificially made from a petroleum derivative and are used as coloring and preservative food additives. A defect in an enzyme called phenol sulfur transferase has been linked to autism. Removing certain foods from autistic children's diets, including foods with colorants and preservatives, and foods with natural salicylates like tomatoes, has been shown to help. Therefore, it is recommended that foods containing colorants, sweeteners, preservatives and sweeteners such as Beta Hydroxy Acids, Butylated Hydroxy Toluene, tertiary Butyl Hydroquinone, as well as foods containing common reactive salicylates such as almonds should be excluded from the diet. Apples, apricots, strawberries, cucumbers, spices such as curry, grapes, raisins, oranges, honey, peaches, peppers and tomatoes should also be restricted [92,108]. Notwithstanding the aforementioned

recommendations, there is a dearth of evidence-based studies demonstrating the efficacy of the Feingold diet in alleviating autism symptoms.

Candida Body Ecology Diet (BED)

Candida albicans is a yeast-like organism that can cause infection in individuals with compromised immune systems. It shows a link between Candida albicans overgrowth in children with autism and a range of behavioral problems such as impaired concentration, aggression and hyperactivity. It can also be linked to symptoms such as headaches, stomach problems, gas pain, fatigue and depression. Antifungal medicines, probiotic supplements and diets low in sugar are used as measures to prevent candida overgrowth. The BED (Body Ecology Diet) was designed with the specific goal of eliminating the overgrowth of candida, promoting gut health, and maintaining an optimal acid/base balance. The BED includes low-acid-forming, easily digestible foods and fermented foods with low or no sugar and starch. BED contains many fermented foods such as raw sauerkraut, kefir and yogurt made with vegetable milk. In addition to being gluten-free, BED is rice, corn and soy-free. Only a few foods such as quinoa, millet, whole wheat and amaranth (when properly soaked) are allowed in the diet [92,109].

Eliminate Allergy Diets

Many children with autism have food sensitivities due to abnormalities in their digestive and immune systems. Undigested carbohydrates or amino acids can cause beneficial bacteria in the gut to react to these elements. In the event that a food allergy or intolerance is suspected, it is recommended that the necessary tests be conducted to identify the underlying issue. Alternatively, avoid consuming the suspect foodstuff for at least two weeks. Following this period, the food item should be reintroduced to ascertain whether allergic symptoms manifest [92].

CONCLUSION

Healthy eating in individuals with ASD can help reduce symptoms, improve behavior, treat other problems and improve the child's quality of life. Given the variability in the presentation of ASD symptoms and the lack of clarity on its underlying cause, a one-size-fits-all nutritional treatment approach may not be feasible. It is thus conceivable that alleviating the symptoms of autism by implementing a dietary regimen designed for co-occurring conditions may also prove advantageous for autism.

Declaration by Authors

Ethical Approval: Not Required
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Sedef Güngör. Nutrition approaches in autism spectrum disorder. *International Journal of Science & Healthcare Research.* 2024; 9(3): 141-157. DOI: *https://doi.org/10.52403/ijshr.20240318*

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