DERLEME REVIEW

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# A Traditional Review of the Role of Nutrition in the Autism Spectrum Disorder

## Otizm Spektrum Bozukluğunda Beslenmenin Rolü Üzerine Geleneksel Bir Derleme

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**ABSTRACT** Autism spectrum disorder (ASD) is a developmental disorder associated with individuals' inability to verbally and non-verbally communicate with their environment. ASD is accompanied by a number of neurological problems and immune disorders and various non-neurological comorbidities such as gastrointestinal system abnormalities. Besides, various nutritional problems, such as food selectivity, food rejection, food allergies and chewing and swallowing problems can be observed in these individuals. In addition to these nutritional problems, elimination diets like gluten-free and/or casein-free diet, specific carbohydrate diet, ketogenic diet and low oxalate diet, applied for therapeutic purposes greatly affect the nutritional status in ASD. Since these diets are aimed at eliminating various nutrients from the diet depending on their content, special care should be taken to ensure that individuals receive sufficient energy and nutrients. When necessary, it may be beneficial to supplement various vitamins and minerals, antioxidants, probiotic and omega-3 fatty acids under expert control. Especially, since children with ASD have inadequate dietary antioxidant intake and highly oxidative stress, antioxidant intake must be followed meticulously. Considering all this, since the effect of nutrition in ASD is very important and there is not enough information yet, it can be said that nutritional interventions should be made depending on the symptoms of the individual with ASD. It should be kept in mind that ASD symptoms can be alleviated with nutritional interventions. In this review, various nutritional problems, different dietary treatments and supplements in individuals with ASD are explained.

**Keywords:** Autism spectrum disorder; diet, food, and nutrition; dietary supplements; antioxidants

**ÖZET** Otizm spektrum bozukluğu (OSB), bireylerin çevreleriyle sözlü ve sözlü olmayan iletişim kuramamaları ile ilişkili bir gelişimsel bozukluktur. OSB'ye birtakım nörolojik ve bağışıklık sistemi problemi ile gastrointestinal sistem anormallikleri gibi çeşitli nörolojik olmayan komorbiditeler eşlik etmektedir. Aynı zamanda bu bireylerde besin seçiciliği, besin reddi, besin alerjileri ve çiğneme ve yutma bozuklukları gibi çeşitli beslenme sorunları da görülebilmektedir. Beslenme sorunlarına ek olarak, tedavi amaçlı uygulanan glutensiz ve/veya kazeinsiz diyet, spesifik karbonhidrat diyeti, ketojenik diyet ve düşük oksalatlı diyet gibi eliminasyon diyetleri de beslenme durumunu büyük ölçüde etkilemektedir. Bu diyetler, içeriklerine bağlı olarak çeşitli besin maddelerini diyetten çıkarmayı amaçladığından, bireylerin yeterli enerji ve besin ögelerini almalarına özen gösterilmelidir. Gerektiğinde çeşitli vitamin ve mineralleri, antioksidanları, probiyotik ve omega-3 yağ asitlerini uzman kontrolünde takviye etmek faydalı olabilir. Özellikle otizmli çocuklarda oksidatif stresin yüksek, buna karşılık diyet antioksidan alımının yetersiz olmasından dolayı diyet antioksidan alımı da titizlikle takip edilmelidir. Tüm bunlar göz önüne alındığında, OSB'de beslenmenin etkisi çok büyüktür; fakat henüz bu alanda yeterli bir literatür bilgisi bulunmadığı için OSB olan bireyin, semptomlarına bağlı olarak beslenme müdahalelerinin yapılması gerektiği ve OSB belirtilerinin, beslenme müdahaleleri ile hafifletilebileceği unutulmamalıdır. Bu derlemede, OSB olan bireylerde görülen çeşitli beslenme sorunları ve uygulanan farklı diyet tedavileri ile destekler açıklanmıştır.

**Anahtar Kelimeler:** Otizm spektrum bozukluğu; diyet, besin ve beslenme; besin destekleri; antioksidanlar

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social disability, language and social interaction deterioration, and in recent years, its prevalence has increased rapidly.[1]

In addition to the symptoms seen in the main diagnostic criteria of ASD; a wide range of neurological comorbidities such as epilepsy, anxiety, mental disability and mood disorders, and many non-neuro-

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logical comorbidities, including blood hyperserotonemia, immune disorder, and gastrointestinal system (GIS), may accompany ASD.[2,3] At the same time, nutritional problems that can lead to inadequate and unbalanced nutrition are often seen in ASD. As a result, in addition to vitamin-mineral deficiencies, the risk of both obesity and malnutrition increases.[4,5] In ASD, gluten-free and/or casein-free diet (GFCF) is used most intensively, but various elimination diets are used for therapeutic purposes.[6] However, applying only these treatment options in ASD may be insufficient to effectively treat ASD, and omega-3, probiotic, vitamin and mineral supplements may be required in individuals with ASD.[7]

ASD, in addition to genetic, environmental and immunological factors, is considered to be a multifactorial disease affected by increased vulnerability to oxidative stress, and it is also reported that antioxidant levels decrease together with the increased oxidative stress in ASD.[8] Antioxidants have potentially beneficial effects in protecting against disease and are considered as part of the treatment of ASD, as it is known that nutrition can play a critical role in protecting against increased oxidative stress and damage caused by free radicals.[9]

In this review, the nutritional problems seen in ASD, dietary treatments and important nutritional supplements are mentioned.

## AUTISM SPECTRUM DISORDER

American child psychiatrist Kanner examined a total of 11 children, 8 boys and 3 girls, in 1943 and found that unlike schizophrenia, those children with ASD exhibit obsessive interest and stereotyped behavior along with serious disorders in communication and social interaction. Regarding to these cases, Kanner defined the concept of ASD for the first time.[10] Accordingly, ASD is a neurodevelopmental disorder characterized by inadequate social-communicative behavior, limited interest and repetitive behaviors.[11]

In the 1990s, the incidence of ASD increased rapidly and still continues to increase.[12] According to the data of the Centers for Disease Control Prevention, the prevalence of ASD was 1 in 68 between 2010 and 2012, and this rate rose to 1 in 59 in 2014.[13,14] ASD prevalence estimates vary by gender and race/ethnicity. In terms of gender, it is known that ASD is more common in boys than in girls, ranging from 2:1 to 6.5:1.[15] In terms of ethnicity, according to prevalence estimates, non-Hispanic white children were more likely to have ASD than non-Hispanic black children and both were compared to Hispanic children.[14]

## ETIOLOGY OF AUTISM SPECTRUM DISORDER

Various risk factors have been defined for ASD; however, none of them has been proven to be sufficient or necessary for the development of ASD alone.[16] ASD etiology is generally defined as the presence of an environmental impact with genetic predisposition.[17] Genetic factors are an important risk factor in the development of ASD, as shown in studies with families of individuals with ASD. The risk of recurrence is higher (about 5-6%) when there is an older sibling with ASD, also when there are 2 children with ASD in the family, it is higher.[15,18] However, genetic factors alone cannot explain this disease, which develops in a relatively short period of 10-20 years; therefore, environmental factors are likely to explain a significant portion of the increased prevalence of ASD.[19] Air pollution, pesticides, endocrine disrupting chemicals and exposure to heavy metals are examples for these environmental factors.[20] In addition, it is suggested that gestational factors that may affect neurodevelopment, such as exposure to chemicals and complications during pregnancy, increase the risk of ASD.[21,22] Although there are several studies showing that mumps, measles and rubella vaccines, thiomersal-containing vaccines or recurrent vaccination can also cause ASD, there is no definitive evidence yet.[23,24]

## NUTRITION PROBLEMS IN AUTISM SPECTRUM DISORDER

Nutritional problems are obvious problems for children with developmental delays; however, due to the absence of universally accepted definitions or the current classification system for eating problems, there are difficulties in identifying such problems.[25]

While nutritional problems typically occur in 25-35% of developing children, this prevalence is estimated to be 90% in ASD.[26] Some reasons such as concentration, impulsivity, fear of innovation, sensory disorders, social compliance deficiencies and food intolerance have been suggested for the prevalence of nutritional problems in children with ASD.[27] Nutritional problems in children with ASD can be collected under the following headings; food selectivity (depending on the type and texture), food rejection, chewing and swallowing problems, food allergies and pica.[5,28,29]

### FOOD SELECTIVITY

Food selectivity is seen as an important problem for many children with ASD and may occur due to a number of factors. Some of these factors can be counted as the taste, texture, shape, color and temperature of the food, as well as the color and shape of the packaging, the layout of the dishes and even the types of utensils used.[30] Field et al. have examined food selectivity in two groups: according to the texture and type of food in general and made the definition of these groups. Accordingly, *food selectivity according to the texture of the food*, as a refusal to consume the developmentally appropriate food tissues; *selectivity by type* is defined as the consumption of a limited variety of nutrients that are not nutritionally appropriate. Children with selectivity by type are limited to eating only a few different foods and often refuse to eat all food groups.[28]

### FOOD REJECTION

Various behavioral problems seen in individuals with ASD also play an important role in nutritional habits and these children tend to refuse certain foods in their nutritional habits.[30] Food rejection has been defined as the rejection of all or many of the foods offered, and therefore, food rejection causes the child not to consume enough food to meet their energy or nutritional needs.[28]

### FOOD ALLERGIES

It is known that GIS problems are frequently experienced in ASD and some behavioral symptoms are associated with GIS problems. Following the elimination of some nutrients in the diet of children with ASD who experience these problems, there may be an improvement in some behaviors in addition to the improvement of GIS symptoms. Therefore, it is thought that food allergy may affect the behavioral symptoms observed in some children with ASD.[31] However, although GIS disorders are more common in children with ASD than those with typical development, epidemiological evidence for the relationship between food allergy and ASD in humans is limited.[32,33] Besides, limited evidence suggests that food allergy is associated with increased nervousness and poor functional results in ASD and that exclusion of hyperalergenic foods may improve some behavioral problems in children with ASD.[31,34]

### CHEWING AND/OR SWALLOWING PROBLEMS

Nutritional skills go through a rapid development process in early childhood as well as general development and growth, and adequate nutrition and swallowing skills are important to ensure that children meet their increasing nutritional needs as they grow.[35] Chewing and swallowing deficiencies in children; may be due to the deficiencies in oral motor skills, sensory awareness and perception.[36]

## DIETARY INTERVENTIONS IN AUTISM SPECTRUM DISORDER

When dealing with ASD, it is crucial to make regulations on the optimal diet, because a proper dietary intervention can help alleviate the symptoms of the disease quickly. Reducing the consumption of some foods and nutrients is associated with the reduction of some diseases such as inflammatory bowel disease, food intolerance, allergies and infections, which are associated with GIS symptoms in patients.[7]

In general, there are no dietary treatments for ASD with proven efficacy, although other diets, especially GFCF, are popular among patients and clinicians. However, treatment may need to be continued for several months before observable improvements are seen, and therefore, patients' families should be cautioned not to expect "miracle cure".

### GLUTEN-FREE AND/OR CASEIN-FREE DIET

GFCF essentially consists of removing both gluten and casein types of proteins (found in wheat, barley, rye, and milk products, respectively) from the diet of

children with ASD. The main reason for following this diet is related to opiod excess theory. After it has been revealed that gluten and casein, one of the food proteins, are metabolized to glutenomorphine (gliadomorphine) and casomorphine, a theory called opiod excess theory has been proposed, which is thought to affect ASD symptoms.[37] According to this theory, increased intestinal permeability, also known as "leaky gut syndrome" in ASD, causes glutenomorphine and casomorphine peptides to pass through the intestinal membrane, enter the bloodstream and cross the blood-brain barrier, which affects the endogenous opiate system and nerve conduction within the nervous system.[38] These peptides then bind to opiate receptors located in the central nervous system, adversely affecting neurotransmission. As a result, after gluten and casein consumption in ASD, it is expected that behavior problems and some GIS symptoms will increase due to this pathway.[39] This opioid excess theory is the most common among the theories explaining the link between diet and treatment of behavioral problems in individuals with ASD.[40]

According to the theory of opioid excess, it is suggested that symptoms may improve if opioids can be prevented or blocked from reaching the brain. That is, removing gluten and casein from the diet of an individual with ASD can break the chain of events by reducing the level of opioids produced by the body, improving behavior problems and some symptoms.[39] See Figure 1.[39]

## SPECIFIC CARBOHYDRATE DIET

According to the theory underlying the specific carbohydrate diet, monosaccharides are easier to digest than disaccharides and polysaccharides, and therefore children with ASD and GIS symptoms can benefit from the monosaccharide diet. Disaccharides and complex carbohydrates are fermented here as they pass into the large intestine without being digested and absorbed, causing excessive proliferation of pathogenic bacteria with excessive gas problems, distension, diarrhea, constipation. The main purpose of this diet is to restore the normal functioning of the intestines and prevent the development of pathogenic microorganisms in the intestine.[41]

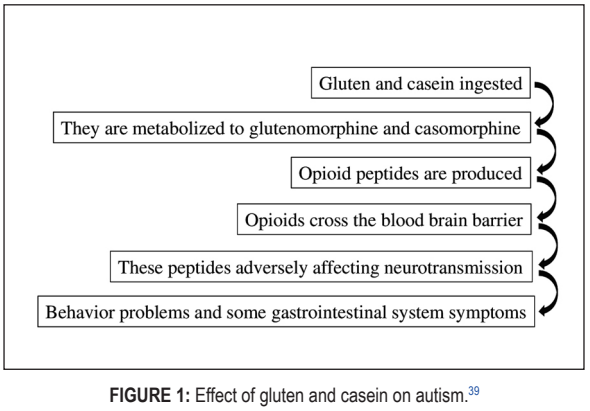


**FIGURE 1:** Effect of gluten and casein on autism.[39]

## KETOGENIC DIET

In addition to epilepsy, an important medical complication with a high risk in developing individuals with ASD, ASD is often accompanied by epilepsy-related syndromes such as Dravet syndrome, Landau-Kleffner syndrome and tuberous sclerosis complex.[42-44] This affects approximately 12% of patients in childhood and 26% in adolescence.[45] ASD is also accompanied by mitochondrial dysfunction, although it is at different levels.[46] Therefore, given the beneficial effects of the ketogenic diet on epilepsy and mitochondrial dysfunction, it is reported that its use in ASD has the potential to improve some of the symptoms associated with ASD.[47]

In this diet, while maintaining normal protein intake, the vast majority of carbohydrates are removed from the diet and replaced by a high-fat concentration. In this way, this diet initiates a state that mimics carbohydrate hunger. The target lipid: nonlipid ratio in the ketogenic diet is between 4:1 and 2:1, and the higher ratio shows more effect.[48]

## LOW OXALATE DIET

It is thought that hyperoxalemia and hyperoxaluria may play a role in the pathogenesis of ASD. In a study conducted to examine oxalate metabolism in these children, the level of oxalate was measured 2.5 times in urine and 3 times in plasma in children with ASD compared to the control group.[49] However, it is uncertain whether this is a problem caused by kidney excretion, intestinal absorption, or both, or whether oxalate can cross the blood brain barrier and affect central nervous system function in ASD.[49] However, it seems likely that it may impair the neurological development of the

child and increase various clinical symptoms by causing abnormalities in the nervous system.[7]

## NUTRITIONAL SUPPLEMENTS USED IN AUTISM SPECTRUM DISORDER

### VITAMINS AND MINERALS

Vitamin and mineral supplements are considered as an adjunct therapy in improving the nutritional and metabolic status of children with ASD and reducing their symptoms.[50] Since nutritional deficiencies in ASD can vary widely, it is expected that the nutritional supplement to be used will differ accordingly.

There is strong evidence that vitamin D has the potential to significantly improve ASD symptoms.[51] In a study on vitamin D, 106 patients with vitamin D deficiency were supplemented with vitamin $D_3$ for 3 months and as a result, 80.7% of the participants who completed the 3-month daily vitamin D treatment showed a significant improvement in their stereotypic and abnormal behavior, eye contact and attention span.[52]

An 8-year-old child with ASD who had vitamin A deficiency and consumed only water with fried potato had a significant corneal improvement after a month of multivitamin treatment.[53] In a 30-week double-blind, placebo-controlled study that investigates the efficacy of ascorbic acid in children with ASD as pharmacological treatment, the children were divided into two groups randomly with a cross-treatment design in the form of ascorbate-ascorbate-placebo or ascorbate-placebo-ascorbate in three periods of 10 weeks.[54] As a result, it was shown that the group taking vitamin C after the placebo had an improvement in social, emotional, sensory and language use areas, while there was a worsening in the group receiving the placebo after vitamin C ($p<0.05$).

The application of vitamin and mineral supplements requires only a few minutes a day compared to other treatments, and they are relatively cheap and safe. Although it may not benefit all individuals with ASD, it has been observed that a significant portion of the improvement can be seen after only three months and that long-term use is safe. For this reason, vitamin and mineral supplements are considered as adjunctive therapy in individuals with ASD and can be used easily with other treatments.[50]

### ANTIOXIDANT

Although some vitamins and minerals are antioxidants, it is extremely important to emphasize the importance of antioxidants against oxidative stress seen in ASD for various reasons and to underline the role of antioxidants in the treatment of ASD.

In addition to a wide variety of problems, many comorbidities accompany the diagnostic criteria of ASD, including mitochondrial dysfunction.[2,3,55] Increased lactate, pyruvate and alanine levels in blood, urine and/or cerebrospinal fluid, serum carnitine deficiency and/or increased oxidative stress are peripheral markers of mitochondrial dysfunction in the vast majority of individuals with ASD. Mitochondrial dysfunction is a reason of oxidative stress, and increasing evidence suggests the role of oxidative stress in the emergence and clinical development of ASD.[56,57] Because the brain is relatively more sensitive to oxidative damage and plays a role in the pathogenesis of major psychiatric disorders.[58] Understanding the role of oxidative stress in ASD can illuminate the environmental, pathophysiology and genetic factors in ASD, and help to find out new treatments and actions to be taken. The potential mechanism of oxidative stress in ASD is shown in Figure 2.[59]

In response to increased oxidative stress in ASD, there is a decrease in antioxidant defense. It is observed that endogenous and exogenous antioxidant capacities of individuals with ASD have reduced. Individuals with ASD have been reported to have significantly lower glutathione peroxidase, superoxide dismutase and catalase activities compared to controls.[60,61] Similarly, it was found that the levels of exogenous antioxidant vitamin A, vitamin C and vitamin E in erythrocytes and plasma levels of zinc and selenium decreased.[62]

Interventions to reduce oxidative damage may offer an opportunity for improvement in the neurodevelopmental area in individuals with ASD. Therefore, increasing the antioxidant capacity in ASD, and using an antioxidant supplement when necessary may contribute to the reduction of ASD-specific behaviors due to the effect of antioxidants in reducing oxidative stress.[57,63-65]

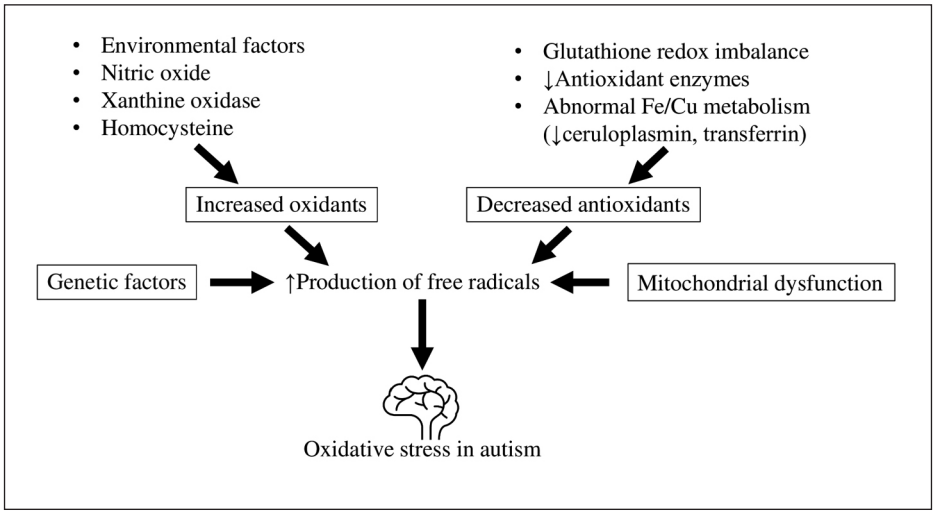


**FIGURE 2:** The potential mechanism of oxidative stress in autism.[59]

## PROBIOTICS

The purpose of the use of probiotics in ASD is to restore the healthy balance of the intestinal microbiota that has changed in ASD.[66] Because the majority of children with ASD have GIS dysfunction, activation of the mucosal immune response and abnormal intestinal microbiota are frequently observed in these children. Therefore, the application of probiotic bacteria in ASD is considered as a therapeutic tool for the recovery of normal intestinal microbiota, the reduction of inflammation, the recovery of epithelial barrier function and the improvement of various behavioral problems.[67]

## OMEGA-3 FATTY ACIDS

Omega-3 fatty acids which have three main types; alpha-linolenic acid, docosahexaenoic acid (DHA) and eicosapentaenoic acid, are called essential fatty acids.[68,69] Omega-3 fatty acids are one of the most commonly used nutritional supplements in ASD. Although the potential mechanism of action of omega-3 fatty acids to improve some symptoms seen in ASD is unknown, studies show that this fatty acid is necessary for the growth and functional development of the brain, as the nerve tissue contains high concentrations of DHA.[69]

# CONCLUSION

Since the cause and solution of some symptoms seen in ASD are closely related to nutrition, it is required that keeping the nutrition of individuals with ASD under constant monitoring. Today, many diets can be used to treat ASD; however, no diet has yet been proven to be effective in the treatment of ASD. At the same time, it should be kept in mind that nutritional supplements can be made if deemed necessary by experts in order to prevent various nutrient deficiencies that may occur after nutritional problems, if an adequate and balanced diet cannot be provided. In particular, it should be underlined that the antioxidant capacity should be increased due to increased oxidative stress. In this way, improving various complications related to ASD seems possible. As a result, it can be said each individual with ASD should be evaluated individually, and accompanying nutritional problems should be intervened.

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*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

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