

Medical Nutrition Therapy Approaches in Children with Autism Spectrum Disorder

Otizm Spektrum Bozukluğu Olan Çocuklarda Tıbbi Beslenme Tedavisi Yaklaşımları

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that occurs in the early stages of development, characterized by limitations in social communication and interaction behaviors, repetitive limiting behaviors, and limited interests. Nutritional problems and gastrointestinal complaints seen in ASD have been known since the first diagnosis of the disease and are considered a feature of the disease. It is known that children with ASD have feeding problems five times more often than children with normal development. The most common nutritional problems seen in children with ASD are food selectivity, difficulty in eating skills, selective, strange, and unusual eating behavior, sensitivity to a particular presentation of food, avoidance of new foods, excessive and persistent intake of one type of food and meal time behavioral problems. Dietary approaches such as gluten-free, casein-free, ketogenic, special carbohydrate, Feingold, Candida body ecology, and eliminated allergy diets are applied. However, the evidence for these practices is limited. Therefore, it is recommended to monitor children with ASD in terms of inadequate and unbalanced nutrition and to consider feeding problems and malnutrition in applying restrictive and special diets.

Keywords: Autism, nutrition, diet

ÖZET

Otizm spektrum bozukluğu (OSB), gelişimin erken evrelerinde ortaya çıkan, sosyal iletişim ve etkileşim davranışlarındaki kısıtlamalar, tekrarlayıcı sınırlayıcı davranışlar ve sınırlı ilgilerle karakterize edilen nörogelişimsel bir bozukluktur. OSB'de görülen beslenme sorunları ve gastrointestinal şikayetler, hastalığın ilk tanısından itibaren bilinmekte ve hastalığın bir özelliği olarak kabul edilmektedir. OSB'li çocukların normal gelişim gösteren çocuklara göre beş kat daha fazla beslenme sorunu yaşadıkları bilinmektedir. OSB'li çocuklarda en sık görülen beslenme sorunları, besin seçiciliği, yeme becerisinde güçlük, seçici, garip ve sıra dışı yeme davranışı, belirli bir besin sunumuna karşı duyarlılık, yeni besinlerden kaçınma, bir tür besinin aşırı ve ısrarlı alımı ve yemek zamanı davranış sorunlarıdır. Glutensiz kazeinsiz diyet, ketojenik diyet, özel karbonhidrat diyeti, feingold diyeti, Candida vücut ekolojisi diyeti, elimine alerji diyetleri gibi beslenme yaklaşımları uygulanmaktadır. Ancak, bu uygulamalar için kanıt sınırlıdır. OSB'li çocukların yetersiz ve dengesiz beslenme açısından izlenmesi, kısıtlayıcı ve özel diyetlerin uygulanmasında beslenme sorunları ve yetersiz beslenmenin göz önünde bulundurulması önerilir.

Anahtar Kelimeler: Otizm, beslenme, diyet

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INTRODUCTION

Autism Spectrum Disorder (ASD) is characterized by significant impairment in social interaction and communication with restrictive and repetitive behaviors, interests, or activities.¹ ASD is a heterogeneous group of diseases that are difficult to diagnose and treat due to the lack of precise and clear information about the cause of the neurodevelopmental disorder.² Diagnostic criteria include three primary headings apparent inadequacy in social interaction, qualitative inadequacy in communication, and excessive struggle with repetitive interest.³ ASD is a common neurodevelopmental disease with a rate of approximately 1.7%(1/59) in the United States.⁴ The etiology of autism remains unclear. There are opinions that genetic and environmental factors are associated with autism symptoms.⁵ Genetically based causes such as chromosomal abnormalities and gene defects constitute 10-20% of individuals with autism.⁶ Environmental factors such as radiation, viruses, drug use, tobacco, alcohol, pesticides, endocrine disruptors, heavy metals, air pollution, and micronutrient deficiencies are also thought to play a role in ASD.^{7,8} DSM-5 considers the clinical features of ASD in two dimensions as inadequacy social communication and repetitive ritual behaviors by bringing a dimensional approach. These clinical features begin in early childhood and adversely affect the activities of daily living. Recognizing these clinical features of ASD varies according to the severity of its symptoms, the child's developmental level, and age.⁹ Deficiencies social communication include problems in social and emotional interaction, mutual dialogue, non-verbal communication, and establishing and conducting human relationships.¹⁰ Restricted and repetitive interests, behaviors, and behavior patterns change with age and take on a different forms. Children with ASD tend to play repetitive games with non-functional objects, have repetitive conversations, show no interest in the typical toy and play, and examine or line them up rather than play with toys.¹¹

Medical treatment of ASD

There is no pharmacological method that affects the basic symptoms of ASD. There are intervention methods applied to children with ASD in different approaches. These; evidence-based practices, comprehensive treatment models, alternative and complementary medicine (special nutrition interventions, vitamin-mineral supplements, etc.), and psychotherapeutic

drugs.¹² Drug therapy is frequently used for comorbid psychiatric diagnoses, and behavioral problems accompanying ASD.¹³ Treatment approaches are grouped as pharmacological and educational. The basic approach to alleviate disease-specific symptoms and increase functionality is educational therapies. Educational therapies aim to improve the field of social communication, reduce unwanted behaviors and gain new skills.¹⁴

Medical nutrition therapy of ASD

It has been observed that children with ASD are more exposed to parent-induced dietary restrictions, so parents of these children are more aware of the foods their children consume or should consume. It has also been observed that they make more effort to ensure that their children receive the recommended amount of nutrients.¹⁵ In a cross-sectional study of children with autism, dietary intake of vitamins A, B₁, B₁₂, D, and folate, calcium, magnesium, potassium, iodine, omega-3, omega-6, linoleic acid, and α -linolenic acid was found insufficient.¹⁶ In a study conducted on children with ASD, it was seen that there was suboptimal nutrient intake. Vitamin D, calcium, and bone health should be taken care of.¹⁷ Vitamin B₁₂ and vitamin D deficiency were significantly detected in children with ASD, and no significant difference in folate levels was found in healthy children.¹⁸

Energy

The metabolic and nutritional status of children with autism showed many differences when compared to healthy children. Children with autism have increased biomarkers indicative of oxidative stress and vitamin deficiency; energy transport, suffusion, and detoxification capacity are decreasing. Some of the biomarkers have been associated with autism severity.¹⁹ In a study conducted on children with ASD, it has been observed that children with ASD between the ages of 2-5 are more prone to being overweight and obese, while children between the ages of 5-11 are more prone to being thin. In addition, it was found that children consumed a similar amount of nutrients and those with autism 4-8 years old children received less energy, zinc, and vitamins A and C.²⁰ No change in energy requirement has been reported in OSB.²¹

Carbohydrate

According to studies examining the intake of macronutrients in children with ASD, it has been shown that there is no significant difference compared to healthy children or that macronutrient intake is higher in

children with autism.²⁰⁻²³ Although adequate intake of macronutrients versus insufficient intake of micronutrients is noteworthy, there is inconsistency in the results.²⁴ In some studies, it is reported that children with ASD have insufficient energy, carbohydrate, protein, and fat intake and that they take many vitamins and minerals inadequately due to their intestinal permeability and selective nutritional behaviors.²⁵⁻²⁷

Protein

5-20% of the daily energy intake for three years of age and 10-30% for four or six years of age should be provided from proteins. There needs to be more information about how much of the proteins that children receive should be of vegetable origin and how much of it should be of animal origin.²⁸ It has been shown that the protein intake levels of children with ASD are similar to those of typically developing children.²⁹

The use of camel milk is seen to eliminate or reduce the behavioral problems seen in ASD. Camel milk, which does not contain beta-casein and beta-lactoglobulin, which can lead to cow's milk allergy, is a good source of protein. Camel milk, which is close to breast milk and rich in micronutrients such as calcium, phosphorus, niacin, and iron and strengthens natural immunity, has been thought to be used in the treatment of ASD.^{30, 31} In a double-blind, randomized controlled trial, children aged 2-12 years were given camel milk for two weeks. Compared with the placebo group, significant improvements were observed in the Childhood Autism Rating Scale (CARS), Social Responsiveness Scale (SRS), and Autism Treatment Evaluation Checklist (ATEC) scores in children who received camel milk.³²

Fat

Since omega-3 fatty acid deficiency is seen in children with ASD, it is thought that this deficiency may cause some symptoms caused by ASD and it is estimated that these symptoms will improve with omega-3 fatty acid supplementation as a supplement.⁷ As a result of the examination of 143 articles written on this subject, it was concluded that there is not enough scientific evidence on the effectiveness and safety of the use of omega-3 fatty acid supplements for ASD.³³ In a study, 30 healthy children with ASD and 30 healthy children aged 3-11 years were examined and it was found that PUFA (Linoleic acid, linolenic acid, arachidonic acid, docosahexaenoic acid) levels were significantly lower in children with ASD. In the same study, children with ASD were given two capsules of omega 3 and omega 6 fatty acids twice a day for 3 months. As a result,

improvements in PUFA levels and behavioral problems due to supplement use were observed in 20 children with ASD.³⁴ In another study, 12 individuals with ASD aged 18-40 years were given 0.93 g eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), 5 mg vitamin E fish oil capsules twice daily for 6 weeks. When the behavior of individuals is observed, it is concluded that behavior problems and the incidence of these problems are significantly reduced.³⁵ Fatty acid supplementation is thought to be associated with ASD and other neurological diseases. However, the number of randomized studies on this subject needs to be increased. Since the number of participants and the duration of the experiment vary in the studies conducted, it becomes difficult to interpret the results systematically.³⁶

Vitamins

Levels of vitamins and minerals have been shown in many studies to be low in children with ASD.^{23, 37, 38} It is thought that these deficiencies may be caused by many factors, such as gastrointestinal (GI) problems, dietary restrictions, and causes arising from the immune system.³⁹ These children were found to have deficiencies in cellular methylation and glutathione-mediated antioxidant defense in the metabolic process. It has been suggested that supplementation of vitamin B₁₂, which is a cofactor in the metabolism of methionine in transmethylation transsulfuration metabolism, may increase methylation and antioxidant capacities in these children.⁴⁰ In addition, oxidative stress in ASD has popularized the use of vitamins C and E.⁴¹ In one study, 20 children with ASD aged 3-8 years were given vitamins B₆ and C for 3 months. Improvements in sleep problems and GI problems were seen in children.⁴² In the study investigating the effects of vitamin A supplementation on the intestinal microbiota in children with ASD, plasma retinol levels and the rate of ASD-related *Bacteroidales* increased significantly at the end of six months. However, the relationship between vitamin A and ASD and microbiota has not been explained.⁴³ In a study conducted on a 14-year-old boy with ASD, vitamin B₁₂ levels were found to be low and homocysteine levels high. The child was given 1000 µg of vitamin B₁₂ supplementation for the first 5 days, then 1000 µg of vitamin B₁₂ per month (as an injection once a month) for 8 weeks, and 500 mg of vitamin C and 400 mg of vitamin E daily. According to the results of the study, improvements in eye contact, touch, and walking and decreases in repetitive behaviors were seen in the children.⁴⁴ In another study, children with ASD were

given methylcobalamin by subcutaneous injection and folic acid by oral route. The result of the study was an increase in cysteine and glutathione concentrations and an improvement in autistic behavior.⁴⁵ Although it is thought that the comorbidities and symptoms of ASD can be alleviated with vitamin supplements, more research is needed on this subject.⁴⁶

Mineral

It has been shown in several studies that children with ASD have a higher prevalence of iron deficiency and iron deficiency anemia than other children.⁴⁷⁻⁴⁹ Inadequate dietary iron intake and malabsorption are thought to cause iron deficiency.⁵⁰⁻⁵² Inadequate intake of iron by diet has been associated with frequent food selectivity in ASD.⁵³ Although it is thought that food selectivity leads to nutrient deficiency in ASD, the relationship between nutrient selectivity and nutrient deficiency has not been clearly determined.⁵⁴ A study on children with ASD showed that children with ASD were less likely to take in dairy products and, therefore calcium.¹⁵ It has been suggested that the difference in copper and zinc levels in children with ASD may cause concentration difficulties, excessive mobility, and impulsivity. In one study, it was found that plasma erythrocyte and zinc levels of children with ASD were lower than in healthy children.⁵⁵ Zinc supplement is frequently seen in ASD.⁵⁶ According to a meta-analysis study, it was found that the plasma zinc level of the group with ASD was lower than the control group. However, no relationship was found between zinc levels and autism severity.⁵⁷ It has been suggested that zinc may be an important mineral in the treatment of ASD because metallothionein regulates gene expression and reduces heavy metal toxicity.⁵⁸ Mousain-Bosc, Roche, et al. examined the effects of magnesium and B6 supplementation in pervasive developmental disorders (PDD) and found that 70% of children with PDD aged 1-10 years improved social interaction, communication, abnormal/delayed functioning, and limited stereotyped behaviors.⁵⁹ Although vitamin and mineral supplementation is a recommended intervention for ASD, the number of studies on this subject is small.⁶⁰

Probiotics

Probiotics are thought to contribute to the improvement of ASD-related problems by changing the levels of metabolites that may be harmful in children with ASD.⁶¹ Another hypothesis that probiotics are thought to be beneficial is that healthy gut flora has an effect on the brain and behavior through the gut-brain barrier.

However, the results of studies on this subject are contradictory. In a 2012 study of children with ASD, children were given supplementation containing *Lactobacillus acidophilus* for 2 months. It was found that the ability to focus on work and perform a task increased in the intervention group compared to the control group. However, no significant behavioral differences were found between the two groups.²⁵ Similar results were found in a placebo double-blind controlled study. Positive improvements in fecal microbiota, gut function, and behavior scores were found with the use of probiotics.⁶² According to current studies, neurotransmitters and neuro immune responses in the microbiota-gut-brain axis may be targeted by probiotics, but the therapeutic effects of probiotics cannot be definitively explained. In addition, there is no definitive report on the improvement of ASD symptoms after probiotic treatment. Therefore, more studies on the use of probiotics in ASD are needed.⁶³

Feeding Problems in ASD

Although studies show that the nutritional problems seen in ASD begin with the transition to complementary nutrition, the data on this subject is limited.⁶⁴ Although selective eating is common in both healthy children and children with developmental problems, some researchers say that selective eating may be a preliminary symptom of autism.⁶⁵ Since sensory integration problems are more common in children with ASD, this situation affects children's eating behaviors. Sensory sensitivity, such as consuming foods according to their colors and smelling foods, can be observed.⁶⁶ Compared to parents of healthy children, parents of children with ASD reported that their children had problematic eating behaviors more frequently.¹⁵ It is stated that GIS complaints, which are frequently seen in ASD, can lead to nutritional problems, while nutritional problems can also lead to GIS complaints.^{67, 68} Early recognition of nutritional problems and intervention is very important in terms of obtaining an effective result. Because eating disorders seen at an early age can affect cognitive, behavioral, and motor development and cause different behavioral problems.⁶⁹

Symptoms of the gastrointestinal tract in ASD

According to a meta-analysis study conducted by Berry, Noval et al., it was found that children with autism had 4 times more GI complaints than children with normal development, diarrhea and constipation were three times more common, and abdominal pain

was twice as high.⁷⁰ Food selectivity in children with ASD may cause GI symptoms such as diarrhea, constipation, or exacerbation of symptoms. These problems increase in these children since simple carbohydrate foods such as sugary foods and snacks are preferred, and vegetables and fruits are not preferred much. Carbohydrate-heavy diets are thought to increase the osmotic load and cause diarrhea.⁷¹ Nutritional management is important in the treatment of GI problems. However, there is no guidance on the nutrition of children with ASD. To develop a guideline that can be used in the clinic, it is necessary to bring together nutritionists who will be particularly interested in the nutrition of children with ASD.⁷⁰

Special diets used in the medical nutrition therapy of ASD

Common special nutritional approaches in the therapy of ASD are gluten-free-casein-free diet, ketogenic diet, special carbohydrate diet, Feingold diet, Candida body ecology diet, eliminated allergy diet, and multivitamin, fatty acid, mineral, and probiotic supplements.⁷²

Gluten-free-casein-free diet

The Gluten Free Casein Free (GFCF) diet is widely used to treat autism.⁷³ According to the "Opioid Excess Theory", there are enzyme defects associated with gluten and casein digestion in children with autism. As a result, it is assumed that intestinal permeability increases in children and the child is adversely affected. Opioids, which occur when foods containing gluten and casein cannot be fully digested, increase intestinal permeability, leak into the bloodstream and cross the blood-brain barrier. In addition, neurotransmission and endogenous opiate system may be affected and may cause impairment of central nervous system function.⁷⁴⁻⁷⁷ This theory explains that gluten and casein-based peptides play a role in the etiology of autism and form the basis of GI system problems.⁷⁴ According to the theory, an increase in the level of opioid peptides in the urine can be considered a symptom of autism. Poor nutrition of these peptides can lower the level in urine and improve the behavioral symptoms seen in autism.⁷⁸ In the GFCF diet, all foods and beverages containing gluten and casein protein are excluded from the diet. Gluten is found in wheat, barley, oats, and rye, and casein is found in milk and dairy products.^{79, 80} Although the GFCF diet is widely used, controlled studies demonstrating its effectiveness in the treatment of ASD are limited. A two-stage, 24-month-long single-blind randomized controlled trial of children with autism included 72

Danish children with autism aged 4-11 years. In the first stage, the children were divided into two groups; one group followed the GFCF diet and the other group did not. Participants were tested at baseline, at 8 and 12 months. According to the analyzes made in the 12th month, significant improvements were seen in behavior problems. In the other stage, participants were tested at 24 months. Although the group in the diet intervention plateaued in behavioral problems, it was seen that the improvement continued.⁸¹ In the treatment of ASD, it has been stated that the diet can be applied if an allergy or intolerance to gluten and casein is diagnosed and there are positive improvements in the symptoms of autism with diet therapy.⁸²

Ketogenic diets

Ketogenic therapy has been applied for years in the treatment of epilepsy. The ketogenic diet (KD), which is also a preferred method in the treatment of ASD, is restricted from carbohydrates and has a low protein and high-fat content. In classical KD, the ratio of fat to carbohydrate and protein in grams is 4:1. 90% of dietary calories come from fats.⁸³ Individuals on a ketogenic diet have changes in insulin and leptin levels, a decrease in serum glucose, and an increase in serum ketone levels and mitochondrial functions. The use of ketone bodies as an energy source has been shown to reduce metabolic disorders and symptoms in ASD.⁸⁴ 30 children aged 4-10 years were included in a pilot study, which was conducted prospectively in children with ASD. The children were given the John Radcliffe diet. The content of energy in this diet includes 30% medium-chain fatty acid, 30% fresh cream, 11% saturated fat, 10% protein, and 19% carbohydrate. 40% of the children who participated in the study could not tolerate or adapt to the diet. Positive changes in CARS scores were seen in children who completed the study.⁸⁵ Since the ketogenic diet contains limited amounts of carbohydrates, proteins, and other nutrients, it can adversely affect growth and cause weight loss. The application of this diet is thought-provoking because of the occurrence of eating disorders in children with ASD and their tendency to have low body weight. These symptoms can be reduced by adding thiamine, carnitine, and lipoic acid to the diet. However, it is recommended to evaluate the risks of dyslipidemia, beta-oxidation defect, acidosis, and mitochondrial and cardiovascular diseases that may occur as a side effect of the ketogenic diet.⁸⁴ Although the studies showing that autism symptoms improve with ketogenic diet application in children with ASD with epilepsy are

limited, it is thought to be promising in the treatment of these symptoms.⁸⁶

Special carbohydrate diet

In treating irritable bowel syndrome and celiac disease, the Special Carbohydrate Diet (SCD) is applied to ensure the balance of bacteria in the intestine.⁸⁷

In SCD, only monosaccharides are allowed from carbohydrates, and most disaccharides and polysaccharides are restricted.⁸⁸ Meat, eggs, homemade yogurt, vegetables, fruit oilseeds, and flours of oilseeds are included in the SCD diet.^{87, 88} From cereals, wheat, oats, and rice, processed meats, canned vegetables and fruits, dried legumes, milk and dairy products, tuber vegetables (potato, sweet potato), curry, onion, and garlic powder are limited.⁷⁰ The studies in a four-year-old boy diagnosed with ASD and Fragile X Syndrome investigated SCD efficacy on GI issues. Improvement in GI symptoms was found.⁸⁹ More studies are needed on the effects of SCD on individuals.⁹⁰

Feingold diet

Phenol is an organic compound, and occurs naturally in salicylates. It is also chemically produced from petroleum derivatives and used as a protective and coloring artificial food additive.⁷² It has been observed that preservatives and colorants can cause hyperactivity in children. In addition, phenol sulfur transferase (PST) deficiency has been detected in individuals with ASD. Salicylates are a phenol subgroup that can be difficult to break down at times in individuals with ASD.⁹¹ Dr. Feingold's hypothesis is that hyperactive symptoms decrease with the elimination of nutrient additives.⁹² Therefore, it is recommended to eliminate foods containing protective, coloring, sweetening, flavoring Beta Hydroxy Acids (BHA), Butylated hydroxytoluene (BHT) and tertiary butyl hydroquinone (TBHQ) from the diet. Spices such as almonds, apricots, apples, strawberries, cucumbers, curries, oranges, honey, grapes, raisins, peaches, tomatoes, and peppers with common reactive salicylate content are also restricted.⁷² A semi-experimental study was conducted in the city of Mansoura to investigate the effects of combining the Feingold diet with language education on language skills in children with ASD. However, no effect of diet on the development of language skills of children with ASD was observed.⁹³

Candida body ecology diet (BED)

Candida albicans, a yeast-like fungus, can cause infection, especially in individuals with suppressed immune systems. The excessive increase of *Candida*

albicans in the body has been associated with impaired concentration, hyperactive behaviors, and aggression in children with ASD. In addition, these problems can be seen together with headaches, stomach problems, gas pain, depression, and fatigue. Antifungal drugs, probiotic supplements, and sugar-poor diets are methods applied as preservatives.⁷⁷ BED is applied to prevent the excessive growth of candida, protect intestinal health, and maintain acid-base balance. This diet contains low-acid-forming foods, easily digestible foods without low sugar and starch content, and fermented foods. Pickled varieties from fermented foods, kefir, and yogurt made from non-animal milk are also included in the diet. In addition to being a gluten-free diet, BED does not contain rice, corn, and soy. Quinoa, millet, amaranth, and whole wheat can be consumed by soaking them neatly.⁷²

Eliminated allergy diets

Children with ASD may have food sensitivity due to problems in the digestive and immune systems. Beneficial bacteria in the intestines react to carbohydrates and amino acids that cannot be digested. If a child is suspected of food allergy or intolerance, the necessary tests should be performed, or suspicious foods should be removed from the diet for two weeks, and when the same food is added to the diet again, it should be observed whether there are allergic symptoms. Since allergic foods are removed from the diet with the elimination diet, there may be improvements in the GI tract, behavior, and attention level. Foods excluded from the diet include milk, soy, wheat, fish, shellfish, eggs, nuts, and peanuts.⁷²

Low FODMAP diet

FODMAP stands for "fermented oligo-di-monosaccharide and polyols." Carbohydrates in this group have high osmotic properties. The absorption of short-chain carbohydrates and polyols, which can be fermented at high levels, is poor. In this diet, these carbohydrates, which can ferment, are restricted. Malabsorption and sensitivity to FODMAP group saccharides may lead to GI symptoms. FODMAP group carbohydrates are fermented by bacteria in the intestine and cause gas formation. In case of malabsorption, the volume of water in the colon increases and causes diarrhea.⁹⁴ Foods that are forbidden by a low-FODMAP diet are removed and reintroduced into the diet.⁹⁵ Apples, pears, peaches, apricots, and dried fruits with a high fructose content; because of lactose-containing milk and dairy products; vegetables and fruits containing fructans such as artichokes, cauliflower, onions, okra, leeks,

broccoli, chickpeas, lentils, beans, wheat and rye , artificial sweeteners such as sorbitol and mannitol are restricted in this diet.^{96,97} Although the FODMAP diet has been shown to provide significant reductions in GI complaints in inflammatory bowel diseases such as Irritable Bowel Syndrome (IBS), the data for its use in ASD are insufficient.⁹⁸

CONCLUSION AND RECOMMENDATIONS

In conclusion, although the studies are promising, the evidence of diet practices reduce the severity of ASD is limited. Therefore, it is recommended to monitor children with ASD in terms of inadequate and unbalanced nutrition and to consider feeding problems and malnutrition in applying restrictive and special diets.

Authorship contribution statement

Concept and design: MA, SÇ, ZB

Acquisition of data: MA, SÇ, ZB

Analysis and interpretation of data: MA, SÇ, ZB

Drafting of the manuscript: MA, SÇ, ZB

Critical revision of the manuscript for important intellectual content: MA, SÇ, ZB

Statistical analysis: -

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