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A REVIEW STUDY ON DIETARY IMPLICATIONS IN AUTISM

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ABSTRACT

Background: Autism cases have increased during the past few years. According to 2008 statistics, the incidence of autism in KSA alone is 6:1000, and that in USA is 1:88. By 2010, these figures have escalated from 1:88 to 1:68, i.e. by 29%. The recent researches focus on the effect of dietary deficiencies on metabolic disturbances and developmental disorders. Children with autism spectrum disorder (ASD) may have restrictive and ritualistic behaviors that affect their eating habits. Selective eating has high prevalence in autistic children than the non-autistic. To date, however, most studies lack the statistical power to arm physicians with evidence-based treatment recommendations for managing symptoms of autism with nutrition. However, it is increasingly important for pediatricians and other physicians who manage children with autism to become familiar with the evidence to date on various nutritional approaches. **Objective:** In the present study, we aim to study the role of diet and nutrition in relation to prevention, control and treatment of Autism Spectrum Disorders. **Conclusion:** There are no specific dietary interventions as such that can cure autism, but certain foods have been found to reduce the symptoms in autistic children. Proper nutrition guidelines may play a role in managing the symptoms in these children.

KEYWORDS: Autism Spectrum disorder (ASD); Metabolic alterations in Autism; Gluten Free Casein Free Elimination Diet; Ketogenic Diet, Chanyi; Childhood Autism Rating Scale.

INTRODUCTION

Autism spectrum disorders (ASD) are complex neurological disorders that are characterized by impairment in social interaction and communication with restricted repetitive and stereotyped pattern of behavior, interest and activities.[1] A combination of genetic and/or exposure to environmental toxic factor are stated to be the result of autism.[2] Autism may associate with physical disabilities like tuberous sclerosis, maternal rubella and mental retardation.[3]

Autism cases have increased during the past few years. The incidence of autism in 2008 in USA was 1:88 and in KSA 6:1000.[4] In 2010 data from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network showed increase in the incident of autism in America to1:68. The new data is higher than the data from 2008 (1:88) by 29%. It was also observed that White children were more likely to be identified with ASD than black or Hispanic children. About 1 in 63 white children, 1 in 81 black children, and 1 in 93 Hispanic children were identified with ASD.[5,6]

An observation of children with autism shows that they have particular eating habits that can result in fewer selection of food categories which influence their nutritional state compared to children without autism.[7] Although the etiology of autism remains unknown, the frequently seen dysfunction in the gastrointestinal and immunological systems in children with autism has led to the increasing focus on nutrition and the role it may play in the symptoms of autism.[3] Research studies are looking at the many factors that contribute to the nutritional status of children with autism, including medical and nutritional aspects and behavioral factors.

In the present study, we aim to study the role of diet and nutrition in relation to prevention, control and treatment of ASD. For a systematic review, we have presented the study under the following sub-topics : feeding problems, general nutritional status, dietary implications, additive approach, antioxidant theory, effect of supplements, role of lipids, etc.

General Nutritional status of Autistic children

A longitudinal study conducted in 2014 compared the nutrient and food group intake of autistic children to both typically developing and developmentally delayed children. This study also evaluated the overall diet quality and the impact of diet restriction. The study exhibited differences in average intake of some nutrients between autism and typical controls, only calcium and dairy were also less likely to be consumed in adequate amounts by the autism group. Intentional diet restriction accounted for most of the differences between autism and typical controls. There was no significant difference on any dietary measures between autistic and with other developmental delay children. All groups had inadequate fiber, vitamin D, and vegetable intake. Inadequate intake

of folate, grains, and dairy was noted for the autism subgroup with intentional diet restrictions. This study also reported significantly worse Healthy Eating Index-2005 scores for children in the autism group not following a restricted diet, than those following a restricted diet and typical controls. These differences however were not nutritionally significant, hence when evaluating nutritional adequacy of children with autism, special consideration should be given to calcium, folate, dairy, and grains. It was suggested that the diets of all autistic children should be evaluated for idiosyncratic deficiencies due to unique dietary patterns.[8]

In a study done in 2011, the nutritional and metabolic status of autistic children were compared with that of neurotypical children and investigated the possible association of autism severity with biomarkers. The study was conducted on 55 autistic children of ages 5-16 years compared with non-sibling, neurotypical controls in the same age, gender and geographical distribution. Neither group had taken any vitamin/mineral supplements in the two months prior to sample collection. Autism severity was assessed using the Pervasive Development Disorder Behavior Inventory (PDD-BI), Autism Treatment Evaluation Checklist (ATEC), and Severity of Autism Scale (SAS). This study measured the vitamins, biomarkers of vitamin status, minerals, plasma amino acids, plasma glutathione, and biomarkers of oxidative stress, methylation, sulfation and energy production. It was observed that the autism group had many statistically significant differences in their nutritional and metabolic status, including biomarkers indicative of vitamin insufficiency, increased oxidative stress, reduced capacity for energy transport, sulfation and detoxification. Several of the biomarker groups were significantly associated with variations in the severity of autism. These nutritional and metabolic differences are generally in agreement with other published results and are likely amenable to nutritional supplementation. Research investigating treatment and its relationship to the co-morbidities and etiology of autism is warranted.[9]
A study done in china in 2013 on 70 children aged 4-6 compared the nutritional status of autistic children with that of typically developing children. The data obtained highlight the parent's questionnaire regarding the eating behavior and gastrointestinal symptoms of their children, anthropometric data, biochemical assessment, physical examination for nutrient deficiencies and food diary. In both groups levels of vitamins A and B_6, Zn and Ca intakes were <80 % of the dietary reference intakes. In addition, the proportions of vitamin C and Ca intake deficiencies in the autism group were significantly higher than those in the control group. Zn level was less than the normal reference range in both the groups. Serum Ca, vitamin A and folate levels in children with autism were significantly lower when compared with children without autism. According to the anthropometric data, the mean BMI, weight-for-height score and BMI for age score of children with autism were significantly higher than those of the typically developing children. Thus, nutritional inadequacies were observed in children with autism and typically developing children in China, and which were, however, more pronounced among children with autism.[7]

Metabolic Alterations

Over recent years, greater recognition has been paid to the myriad co morbidities that accompany autism and that may contribute to the fluctuations in the severity of autistic symptoms, most notably aggression, hyperactivity, and lack of attention. Among these co morbidities, dysfunctions of the gastrointestinal and immunological systems have garnered particular attention because of their common occurrence in children with autism.[4,5] Studies report that between 30% and 80% of autistic children have symptoms of gastrointestinal dysfunction of which diarrhea is the most common, followed by constipation, abdominal distention, and pain.[6] Dysfunctions in immunological systems have also been noted in autistic children, presenting as food allergies or metabolic abnormalities.
An abnormality in the digestive and/or immune systems in many autistic children cause food sensitivities. Partially digested food can cause immune reaction in these children accompanied with changes in behavior, that may be attributed to pain and discomfort caused by reactions to food allergens. Children with autism should be screened for any enzymes abnormalities. Several studies suggest that some of the autistic children have low level or less active enzymes like disaccharidase enzymes.[10]

Feeding problems in Autistic Children

Children with autism spectrum disorder (ASD) may have restrictive and ritualistic behaviors that affect their eating habits. Selective eating has high prevalence in autistic children than in non-autistic. According to Dr. Eric Levey, medical director of Pediatric Feeding Disorders Continuum at the Kennedy Krieger Institute, feeding problems in children with ASD can range from mild to severe. Most feeding problems are often mild at the onset, but in some cases become severe because parents have difficulty managing their child's challenging behavior and end up enabling them.

Children with autism who are picky eaters limit themselves to five foods or fewer in some extreme cases, according to Melissa Olive, a psychologist who treats Autistic children with feeding disorders at her practice in New Haven, Connecticut. Parents should know whether their children have feeding problem because of compulsive behaviors or because of any other reason. Some autistic children have feeding problem because of motor and sensory challenges, for example; they can't tolerate loud noises that come from food or have trouble with chewing and swallowing. So they may prefer smooth or soft foods.[11]

Impact of Micronutrient Deficiencies

The intake of calories and protein are not affected in children with autism, on other hand the vitamin and mineral intake may appear inadequate in children with autism; some of these minerals are vitamin A, K, D and cesium.[8] Many health problems are caused by insufficient intake of vitamin and mineral, like anemia caused by low intake of iron, hypothyroidism by low intake of iodine and rickets by low intake of calcium and/or vitamin D deficiency. The recent researches focus on the effect of these deficiencies on metabolic disturbances and developmental disorders like learning disorder and intellectual development.[10]

The active from of vitamin D is known to have a role in regulation of immune function. It affects the activation of the activated helper to T cell, regulatory T cell and activated B cell. This discovery has linked vitamin D to autoimmune disorders. There is an increase in the autoimmune frequency in autistic families. Moreover autoimmunity may be one of the causes of autism in some families.[11]

There seems to be a difference in the nutritional and metabolic status in patients with autism compared to non- autistic.

Role of Specialized Diets

One of the most popular and famous diet suggested for autism is Gluten Free, Casein Free (GFCF) elimination diet. This is based on elimination of any food that contains gluten or casein. Gluten is protein that is wheat, barley and rye. Casein is protein that is present in milk, yogurt and cheese. There are some theories that suggest that there is relation between diet and behavior for autistic children. According to "opoid excess theory of autism", the intake of gluten and casein cause some negative behavior and outcome.[12]

A review done in 2013 focused on the effect of The Gluten-Free, Casein-Free Diet (GFCF). This review had five studies from 1999 to 2012 that were included after being identified to meet the inclusion criteria. Three of these studies reported no positive effect of the dietary intake on behavior or development, even after double blind gluten and casein trials. Only two studies reported some positive effects at the end of 1 year on the diet, but their results may have been impacted by placebo effects and high attrition rates. Regardless its popularity, based on these five well-controlled group studies, the effect of a GFCF diet on behavior is inconclusive at best.[12]

A review done in 2014, to determine the Potential Therapeutic Use of the ketogenic diet (KGD) for autism patients. KGD is used in treatment for individuals with glucose transporter1(GLUT1), pyruvate dehydrogenase (PDH) deficiencies and epilepsy. It's also used in a number of neurological disorders. So, there is recent interest in its possible therapeutic use in autism.

Analysis of a case report indicated that children with ASD treated with a KGD showed decreased seizure frequencies and exhibited behavioral improvements like enhanced learning abilities and social skills. The KGD could benefit individuals with ASD affected with epileptic episodes as well as those with either PDH or mild respiratory chain (RC) complex deficiencies. Given that the mechanism of action of the KGD is not fully understood, caution should be exercised in ASD cases lacking a careful biochemical and metabolic characterization to avoid deleterious side effects or refractory outcomes.[13]

In this review they examined evidence suggestive that a gluten-free (GF), casein-free (CF), or gluten- and casein-free diet (GFCF) have positive effect on the symptoms and can improve developmental outcome in some cases of autism spectrum conditions. Although not wholly favorable, the majority of published studies indicate statistically significant positive changes to symptom presentation following dietary intervention Experimental studies on the use of a GFD, CFD, or combinatorial GFCF diet for ASCs have suggested an amelioration of symptoms and improved developmental outcome for at least a proportion of people on the autistic spectrum. Although, various methodological issues potentially biasing results remain which, combined with a lack of generalizable information on mode of action and best-responder data, have limited the impact of such findings over the years.[14]

Study aimed to determine the efficacy of gluten and/or casein free diets as an intervention to improve behavior, cognitive and social functioning in individuals with autism. All randomised controlled trials (RCT) involving programmes which eliminated gluten, casein or both gluten and casein from the diets of individuals diagnosed with an autistic spectrum disorder were selected. Two small RCTs were identified. No meta-analysis was possible. There were only three significant treatment methods that had a positive impact on the overall autistic traits, mean difference, social isolation and overall ability to communicate and interact. The other three outcomes showed no significant difference between the treatment and control group and they were unable to calculate mean differences for ten outcomes because the data were skewed. No outcomes were reported for the benefits including harms.

Authors conclude that Current evidence for efficacy of these diets is poor.**[15]**

Additive approach and considerations

The concept of "food as medicine" has been well applied as clinical intervention for promoting mental and physical health within the Shaolin medical approach (Chanyi). It is believed that inappropriate intake of certain types of food may have harmful effects on physical health, mental state, and cognitive functions of human beings. The Chanyi proposed that excessive

intake of hot and spicy foods (including all meats, seafood, eggs, ginger, garlic, spring onions, Chinese chives, and chili food) with high-fat and high-energy content will generate excessive heat inside the body and cause blood and Qi stagnation, which in turn, result in both physical and mental illnesses. So, the Chanyi recommends the use of a natural and balanced vegetarian diet and reduction of the intake of and spicy foods. A study in 2012 aimed to investigate the potential effect of a *Shaolin*-medicine-based dietary modification on improving executive functions and behavioral symptoms of ASD and exploring the possible underlying neurophysiological mechanisms. This study was carried for over one month on 24 children. Experimental group were autistic children who receive dietary modification and the control group were autistic children with no dietary modification.

Each child was assessed on his/her executive functions, behavioral problems based on parental ratings, and event-related electroencephalography (EEG) activity during a response-monitoring task before and after the one month. The experimental group demonstrated significantly improved mental flexibility and inhibitory control after the diet modification, which continued to have a large effect size within the low-functioning subgroup. Such improvements coincided with positive evaluations by their parents on social communication abilities and flexible inhibitory control of daily behaviors and significantly enhanced event-related EEG activity at the rostral and subgenual anterior cingulate cortex. In contrast, the control group did not show any significant improvements. These positive outcomes of a one-month dietary modification on children with ASD have implicated its potential clinical applicability for patients with executive function deficits.[16]

The Antioxidant theory

Some studies have suggested the relation of oxidative stress to the development of autism.[4] Oxidative stress is the imbalance between the reactive oxygen species(ROS) and the antioxidant.[6] The ROS can cause damage to the body cell.[3] The antioxidant activity is the defense mechanism against the oxidative stress.[4] One of these biomarkers is the indicative of vitamin E insufficiency.[2] In 2010, a study done on subgroup of autistic patients with different Social Responsiveness Scale (SRS) and Childhood Autism Rating Scale (CARS) scores, measured the concentration of two toxic heavy metals lead (Pb) and mercury (Hg) in red blood cell. While glutathione-s-transferase (GST) and vitamin E, as enzymatic and non-enzymatic antioxidants, respectively, were measured in the plasma of subgroups of autistic patients with different Social Responsiveness Scale (SRS) and Childhood Autism Rating Scale (CARS) scores. The results were compared to the healthy control with the same age and gender.

The data shows that compared to healthy control, autistic children had significantly higher Pb and Hg levels and lower GST activity and vitamin E concentrations. They correlated the level of heavy metals Hg and Pb, GST and vitamin E with the severity of the social and cognitive impairment measures (SRS and CARS). This study confirms earlier studies that implicate toxic metal accumulation as a consequence of impaired detoxification in autism and provides insight into the etiological mechanism of autism.[2]

A study in 2013 aimed to evaluate the effect of camel milk consumption on oxidative stress biomarker in autistic children. They measured the plasma levels of glutathione, superoxide dismutase, and myeloperoxidase before and 2 weeks after camel milk consumption, using the ELISA technique. All the measurements showed significant increase after the consumption of camel milk consumption these findings suggest that camel milk could play an important role in decreasing oxidative stress by alteration of antioxidant enzymes and nonenzymatic antioxidant molecules levels, as well as the improvement of autistic behavior as demonstrated by the improved Childhood Autism Rating Scale (CARS).[4]

Effect of supplementation in autism

A number of nutritional interventions that focus on adding supplements to the diets of autistic children have been investigated over the years. A 2006 study reported that 74% of families with autistic children were using CAMs, and of these over 54% were using some type of nutritional management such as modified diets and nutritional supplements.[3] These include supplementation with a variety of vitamins and minerals including vitamin B_6/magnesium, vitamin C, vitamin D, vitamin B_{12}, dietary fatty acids (omega-3, cod liver oil), melatonin, folic acid, probiotics, L-carnitine, iron, and zinc and copper.[3,4,7] Evidence on a number of these supplements is scarce and ongoing. Table 1 provides a list of the current evidence on the most studied supplements.[5-7]

A randomized, double-blind, placebo-controlled study was conducted in over three month course on vitamin/mineral treatment on 141 children and adults with autism, and pre and post symptoms of autism were assessed. None of the participants had taken a vitamin/mineral supplement in the two months prior to the start of the study. For a subset of the participants (53 children ages 5-16) pre and post measurements of nutritional and metabolic status were also conducted.

Oral vitamin/mineral supplementation is beneficial in improving the nutritional and metabolic status of children with autism, including improvements in methylation, glutathione, oxidative stress, sulfation, ATP, NADH, and NADPH. The supplement group had significantly greater improvements than did the placebo group on the PGI-R Average Change. This suggests that a vitamin/mineral supplement is a reasonable adjunct therapy to consider for most children and adults with autism.

The vitamin/mineral supplement was generally well-tolerated, and individually titrated to optimum benefit. Levels of many vitamins, minerals, and biomarkers improved/increased showing good compliance and absorption.[9]

Children with autism spectrum disorder (ASD) are reported to have decreased bone cortical thickness (BCT). Vitamin D plays an important physiological role in bone growth and development, so deficiency of vitamin D could contribute to decreased BCT. The goal of this study was to compare plasma 25(OH)D concentration in three groups of Caucasian male's age 4 to 8 years old. One of the groups is 40 autistic children with an unrestricted diet, the other is 9 autistic children with casein-free diet and the last one is unaffected 40 controls. No significant group differences were observed. However, a total of 54 (61%) of the children in the entire cohort had a plasma 25(OH)D concentration of less than 20ng/mL, similar to findings of low 25(OH)D concentrations in population-based studies. Children with ASD should be monitored for vitamin D deficiency.[20]

The results of a metallomics study in which scalp hair concentrations of 26 trace elements were examined for 1,967 autistic children (1,553 males and 414 females aged 0–15 years-old), found a deficiency in zinc in 29.7% of the subject and 17.6%in magnesium. 43.5% of zinc deficiency estimated in male and 52.5% in female infantile subjects aged 0–3 years-old. 17.2%, 168 8.5% and 94 4.8% individuals were found to suffer from high burdens of aluminum, cadmium and lead, respectively, and 2.8% or less from mercury and arsenic. High toxic metal burdens were more frequently observed in the infants aged 0–3 years-old, whose incidence rates were 20.6%, 12.1%, 7.5%, 3.2% and 2.3% for aluminum, cadmium, lead, arsenic and mercury, respectively.

These findings suggest that infantile zinc- and magnesium-deficiency and/or toxic metal burdens may be critical and induce epigenetic alterations in the genes and genetic regulation mechanisms of neurodevelopment in the autistic children, and demonstrate that a time factor "infantile window" is also critical for neurodevelopment and probably for therapy. Thus, early metallomics analysis may lead to early screening/estimation and treatment/prevention for the autistic neurodevelopment disorders.[21]

Autism spectrum disorder (ASD) is often accompanied by self-injurious behavior (SIB), aggression, and tantrums, symptoms that have reportedly improved with micronutrient (vitamins and minerals) treatment. This study took advantage of naturally occurring differences in parental preferences for treatment approaches. The micronutrient group 44 autistic children aged 2-28 years were asked for treatment without pharmaceuticals and the result to compare to medical group which are 44 similar children treated with conventional treatment.

Both groups improved on both the Childhood Autism Rating Scale and the Childhood Psychiatric Rating Scale. Both groups also exhibited significant decreases in total Aberrant Behavior Checklist scores, but the micronutrient group's improvement was significantly greater. SIB Intensity was lower in the micronutrient group at the end of the study, and improvement on the Clinical Global Impressions scale was greater for the micronutrient group. It is difficult to determine whether the observed changes were exerted through improvement in mood disorder or through an independent effect on autistic disorder. There were some advantages to treatment with micronutrients—lower activity level, less social withdrawal, less anger, better spontaneity with the examiner, less irritability, lower intensity SIB, markedly fewer adverse events, and less weight gain. Advantages of medication management were insurance coverage, fewer pills, and less frequent dosing.[22]

Role of Dietary Lipids

A study done in 2011 in Saudi Arabia, compared plasma fatty acid profiles in 26 autistic patients with 26 control subjects in the same age to clarify the role of fatty acid in the etiology of autism. Methyl esters of FA were extracted with hexane, and the fatty acid composition of the extract was analyzed on a gas chromatography.

The obtained data proved that fatty acids are altered in the plasma of autistic patients, specifically showing an increase in most of the saturated fatty acids except for propionic acid, and a decrease in most of polyunsaturated fatty acids. The altered fatty acid profile was discussed in relation to oxidative stress, mitochondrial dysfunction and the high lead (Pb) concentration previously reported in Saudi autistic patients. Statistical analysis of the obtained data shows that most of the measured fatty acids were significantly different in autistic patients compared to age -matching controls.

Receiver Operating Characteristic (ROC) curve analysis shows satisfactory values of area under the curve (AUC) which could reflect the high degree of specificity and sensitivity of the altered fatty acids as biomarkers in autistic patients from Saudi Arabia.[11]

According to review study done in 2013 to determine the safety and efficacy of omega-3 fatty acids for autistic patient, from 6 earlier studies that were reviewed, one small randomized controlled trial ($n = 13$) noted non-significant improvements in hyperactivity and stereotypy. The remaining five studies were small, with four reporting improvements in a wide range of outcomes including language and learning skills, parental observations of general health and behavior, a clinician-administered symptom scale, and clinical observations of anxiety. Due to the limitations of evidence from uncontrolled studies and the presence of only one small randomized controlled trial, there is currently insufficient scientific evidence to determine if omega-3 fatty acids are safe or effective for ASD.[23]

CONCLUSION

Reviewing the previous studies from earlier reviews, we have drawn the following conclusions. There are no specific dietary interventions as such that can cure autism, but certain food components have been found to reduce the symptoms in several autistic children. Antioxidants like vitamin A, Glutathione and Superoxide dismutase have been found to reduce the oxidative stress that has been suggested to have role in the development of autism.

Autistic children have different plasma fatty acid profiles then neurotypical children, perhaps this could be used as biomarkers for autism. Additionally, propionic acid and short-chain fatty produced by dietary or by enteric bacteria may trigger ASD. Despite much popularity, there is insufficient evidence on the effect and safety of omega-3 fatty acids on autism.

The Ketogenic Diet has not proved its efficiency due to lack in evidence. And there is conflict in role of the GFCF diet, with its effect on autism still inconclusive. Some studies showed improvement of the symptoms but most have no significant difference. Moreover, there is no report on harmfulness of this diet. ***Shaolin***-medicine-based dietary modification showed positive outcomes but it requires more research.

Parents should know and avoid foods that cause allergic reaction to their children. Also, they should know whether their problematic eating habit is from motor and sensory challenges or other behavioral reason so they can handle it properly by providing the appropriate diet to their children if the problem is motor and/or sensory. If the problem were behavioral, the parent should reinforce good feeding habits.

Evidence is accumulating on all these factors that may contribute to the nutritional status of children with autism and the potential connection to the co morbid gastrointestinal and immunological dysfunction in these children. To date, however, most studies lack the statistical power to arm physicians with evidence-based treatment recommendations for managing symptoms of autism with nutrition. However, it is increasingly important for pediatricians and other physicians who manage children with autism to become familiar with the evidence to date on various nutritional approaches. This is highlighted by the high percentage of parents who are using some type of complementary and alternative medicine (CAM) to help their children with autism.

Given the strong and growing interest in nutrition by those who care for children with autism, pediatricians and healthcare professionals should become familiar with evidence on the different nutritional approaches to managing the symptoms of autism. Although no one nutritional approach will work for all children with autism, given the still unknown etiology of autism and its different presentation in each child, there is growing evidence that nutrition may play a role in managing the symptoms in autistic children.

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