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Review Article

**A REVIEW ON ROLE OF VITAMINS AND MINERALS IN
AUTISTIC SPECTRUM DISORDERS****Jimmer Joe, M. Sudha, N. Venkateswaramurthy, R. Sambathkumar.**Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam,
Tamilnadu, India.**Abstract:**

Autism spectrum disorders are a group of developmental disabilities characterized by diminished social interactions and delayed language, behavioural. Vitamin/mineral supplementation is beneficial in improving the nutritional and metabolic status of children with autism. Limited, self-restricted diets, nutritional insufficiency and metabolic imbalances may play a role in autism spectrum disorders (ASD) in children. Vitamin B6 resulted in better eye contact, speech and self-stimulatory behaviour in autistic children. Dimethylglycine (DMG) usually begins to show benefit after 1-4 weeks. Calcium regulation in the body plays a major role in neuronal development and synaptic plasticity. Improved symptoms severity and sensory motor scores in autistic patients possibly due to interaction with dopamine synthesis; Vitamin C also has a strong effect on glutathione. Zinc deficiency disturbances in ASD pathogenesis. Studies showed that most of children showing ASD symptoms had significant lowered zinc levels in their hair. Vitamin A also some marked improvement in autism symptoms, such as language, eye contact, ability to socialize and sleep patterns, were improved.

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INTRODUCTION:

Autism spectrum disorders are one of the genetic disorder found in children. It is characterized by diminished social interactions and delayed language, behavioral disturbances such as self-injurious behaviour, aggressive attitudes in response to routine environmental demands [1]. Enhancements made in the diagnostic techniques within the last few decades have led to the differentiation and variation in traditional use of the term autistic disorder to include autism, Asperger's syndrome, Rett's syndrome, and childhood disintegrative disorder. The ASD begins during the first three years of life and varies with gender in a male female ratio of 5:1 (male: female) [2].

About 85% of the autistic suffer from idiopathic autism where the exact cause of the disease remains is not known. On the other hand, in case of symptomatic or secondary autism the causative factor can be exists only in 15% of the cases [3].

The actual cause of autistic disorder is not clear, because of that its pathophysiology begins early during embryonic stage and preventive measures are hard to take. The different multidimensional causes of autism include genetic factor and heterogeneity, gastrointestinal pathology, autoimmune disorder, inflammation, increase level of oxidative stress, disability of the body to detoxify toxins, dysfunction of mitochondria. Vaccinations and food preservatives are the iatrogenic causes. These factors add to the pathogenicity of ASDs, of which most are interactive. Central nervous system autoimmunity exists in some autistic patients [4]. Oxidative stress caused by the reactive oxygen species is a causative factor for the occurrence and severity of ASDs. Genetic studies shows twins, families and genetic associations have revealed the presence of a high genetic correlation as a cause of autism [5]. 1 in 88 children of United states developed any form of ASD, and the global prevalence of the diseases is remain 1% [5]. In Saudi Arabia, 42,500 confirmed cases of autism were reported in the year 2002. Seizure are also prevalent in 22-30% of children with ASD [6].

Role of Vitamins and Minerals in Autistic disorder

Vitamins and minerals (elements) are vital for human health. The inadequate deficiency of vitamins and minerals due to poor dietary intake contributes as a major factor to many health problems like anemia (low iron content), rickets (calcium and/or vitamin D deficiency), scurvy (vitamin C deficiency) and hypothyroid (low iodine). The relationship between relative metabolic disturbances and

developmental disorders, were also found in recent times. For example those associated with attention deficit disorder, learning disorders, and intellectual development [7,8]. A study in Slovakia found that children with autism had significantly higher levels of vitamin C and beta-carotene, but normal levels of vitamin A and vitamin E, compared to older teen controls [9,10].

Multiple Vitamin-Mineral Supplements

People with autism typically have poor nutritional status. They often have poor digestion (approximately 25 percent have chronic diarrhea; 25 percent have constipation). Many have intestinal inflammatory conditions that limit nutrient absorption [11,12], sometimes beneficial bacteria in the intestines are depleted, so fewer vitamins are produced by these friendly symbionts (vitamin B12, biotin, and vitamin K, in particular) [13]. Multivitamin supplementation is beneficial for both adult and ASD children [14]. Around 50 percent of subjects found decreased levels of vitamins A, B1, B3, and B5, and biotin; minerals selenium, zinc, and magnesium; essential amino acids; and two essential fatty acids (omega-3 eicosapentaenoic acid (EPA) and the omega-6 dihomogammalinolenic acid (DGLA)). Other clinicians report frequent deficiencies of vitamins B6 and B12 and folate. In 2002, Adams reported on a double-blind, placebo-controlled trial supplementing a multivitamin-mineral complex to 16 autistic children for a three months. Levels of vitamins B6 and C in blood were significantly increased, and sleep and bowel patterns (parents' scores) were significantly improved. Multivitamin-mineral supplements for ASD children should not be given with copper because that is the one mineral they have in excess [15].

Vitamin B6 and Magnesium

The active form of Vitamin B6 is pyridoxal-5-phosphate (P5P), is an essential cofactor for a majority of metabolic pathways of neurotransmitters, including serotonin, gamma-aminobutyric acid (GABA), dopamine, epinephrine and norepinephrine. Magnesium is an essential mineral required in large amount for a wide range of enzyme-catalyzed metabolic pathways. While autism is not curable by vitamin B6 are known, many cases of notable improvement have been documented. Heeley and Roberts in 1966, had reported vitamin B6 corrected abnormal tryptophan metabolism in 11 autistic children [16]. In 1968, Bonisch reported vitamin B6 with a dosing range of (100-600 mg per day) improved behavior in 12 of 16 autistic children. Rimland, studies suggests that three of Bonisch's

subjects spoke for the first time while participating in this open trial [17,18].

Dimethylglycine

Dimethylglycine (DMG) is an orthomolecule present in small amounts in foods, and is an important methyl donor with antioxidant character. The study by Kun DMG was administered to 39 autistic children with an age 3-7 years for three months; [19] and benefits were reported for (80%) of the autistic children. Kern and collaborators conducted a four-week, double-blind, placebo-controlled trial on 37 children age 3-11 years [20]. Both the DMG and placebo groups improved but showed no significant difference between the two groups. The short time period of this trial may have been insufficient for the full DMG benefit to emerge. The nutrient TMG (trimethylglycine; betaine) has a third methyl group, and some experts believe it could prove more clinically effective than DMG. It may be that DMG does more for the autistic subject than merely supporting methylation. Both these nutrients may be taken earlier in the day to avoid the rare possibility of interference with sleep. Rimland recommends children be started on DMG at a low intake (60 mg per day with breakfast), then titrated up to 500 mg per day. DMG usually begins to show benefit after 1-4 weeks and, in some occasional cases, the results within the first 24 hours [21]. Although speech is the most consistent benefit, behavior also improves. Seizures have been improved by DMG, an important benefit since an estimated one-third of ASD subjects have seizures by adulthood [22]. Occasionally an ASD child will experience transient hyperactivity; administering folic acid and vitamin B12 with DMG lessens the likelihood of this effect [23].

Folic Acid

Folic acid is essential to numerous metabolic pathways. Several researchers report folic acid has favourable effects on patients with autism associated with fragile X syndrome. LeJeune pioneered folic acid treatment of fragile X and, according to Rimland [17], obtained favourable results on several non-fragile X autistic children by giving relatively large doses of folic acid (0.5-0.7 mg/kg/day). Vitamin B6 and folic acid, supports numerous pathways that sustain and renew the body's tissues. Since folate and folic acid are vital for the primary cellular processes, including DNA replication and protein methylation, it is biologically possible that folic acid intake may affect different conditions positively or negatively depending on the dosing and frequency [24]. Some researchers intended that FR autoimmunity and cerebral folate deficiency play a crucial role in the pathophysiology

of autism spectrum disorders or in a specific subgroup of the autism spectrum [25, 26].

Folic acid has a vital role in the neural development and it also participates in the carbon metabolic pathway, DNA synthesis, cell proliferation, immune function etc [27]. The normal brain development also affected by Folate deficiency through a variety of mechanisms and the deficiency of folic acid during pregnancy has been reported as a risk factor for the offspring to develop ASD [28].

Calcium

Calcium and magnesium deficiency is most common in autistic children [29]. About 22 percent of an autistic children sample had low 24-hour urinary calcium excretion [30]. Calcium regulation in the body plays a major role in neuronal development and synaptic plasticity [31]. Extracellular calcium, is also present on developing neurons and helps to control neurite outgrowth in the developing postnatal brain [32]. Therefore, hypocalcemia in some patients with 22q11-deletion syndrome (22q11DS) may have a harmful effect on neurite outgrowth and synaptogenesis. But there is evidence for dysregulation of calcium in ASD [33]. Indeed, in recent times calcium dysregulation emerged as the most noticeable biological factor in ASD risk when both genetic and environmental factors are taken into consideration [34].

Vitamin C

Vitamin C has its role in a variety of metabolic, antioxidant and bio-synthetic pathways and acts as a cofactor for certain enzymes necessary for neurotransmitter synthesis. In a double-blind trial for 30 weeks, vitamin C (8 g/70 kg body weight/day) improved total symptom severity and sensory motor scores [35]. Vitamin C supplementation may have positive effect on the pathological behaviour with ASD people. It is thought that dysregulation of the brain signalling glutamatergic system is prevented by ascorbic acid. And thereby reduces brain inflammation [36].

Treatment with Ascorbic acid showed a reduction in the symptoms severity of autism. Adams and Holloway studied the effect of moderate-dose multivitamin supplements, containing vitamin C, on autistic symptoms. Lower serum levels of vitamin C were observed in children receiving placebo than in children taking the supplement. It was found that high vitamin C doses may affect sleep disorders and gastrointestinal symptoms in ASD people [37, 38].

Zinc

Zinc is essential for the development and maintenance of organs such as brain, adrenal glands, GI tract, and immune system. Serotonin synthesis which is dependent on zinc-activated enzymes; and it is also needed for antioxidant enzyme activity and other proteins which enhance growth and homeostasis. The experiments with rodents during their breeding found that zinc deficiency in the mother can be passed on to the offspring and negatively influence immunity and brain development [39].

Zinc (Zn) and copper (Cu) may contribute factors in the pathogenesis of ASDs [40, 41]. These elements may also cause changes in the intestinal flora and function in the autistic patients [42]. Malabsorption due to pathological changes in the intestinal mucosa may play a major role in autism. Low intracellular Zn concentration has been associated with DNA damage due to oxidative stress, impairment of antioxidant defences, and may be due to impairment of DNA repair [43]. Importantly Zn is primarily an intracellular nutrient and serum Zn levels can be normal in states of mild deficiencies [44]. Studies showed that most of children showing ASD symptoms had significantly lowered zinc levels in their hair [45]. Also Faber *et al.* recommended the importance of zinc deficiency and the metallothionein detoxification system disturbances in ASD pathogenesis [46]. They hypothesized that plasma zinc/copper ratio may be considered as a one of biomarkers of autism susceptibility in children. It was also reported that supplementation of nutrients, including zinc, during infancy development, can reduce severity of ASD symptoms [45]. There are some reasons showing the GABA role in autism aetiology [47]. GABA levels as a neurotransmitter is reduced in autistic individuals. This amino acid reduction leads to aggressiveness, restlessness, irritability, and seizures [48].

Essential Fatty Acids Essential fatty acids (EFAs) function as homeostatic constituents of cell membranes, helping to relay signal information from outside the cell to the cell interior and are precursors to eicosanoids that influence other cells, similar to hormones. The longer-chain, 20- and 22-carbon species are crucially important for prenatal and postnatal brain development [49]. Biologically, the 18-carbon EFAs linoleic acid (omega-6) and alpha-linolenic acid (omega-3) qualify as vitamins since deficiency states are known. Some adults can generate the longer-chain EFA from the shorter-chain fatty acids, but infants are highly limited in this capacity [50]. Studies conducted deficiency of EFA in autism people are few, but were consistent results. Bradstreet

and Kartzinel found omega-3 fatty acids are also found deficient in nearly 100 percent of ASD cases during various studies. [29] 60% of the dry weight of the brain are made up by fatty acid and 20% are made up by long-chain polyunsaturated fatty acids (PUFA) [51]. Concentration of DHA (omega-3 docosahexaenoic acid) is high at neuronal synapses and positively affect the sodium potassium pump activity in the brain and demonstrating the maintenance of neuronal membrane potentials [52]. Phospholipids are a relevant type of lipid to be studied in case of autism, because of their high availability in the neuronal membranes also their fatty acid composition is known to reflect long-term fat uptake and storage [53, 54].

DHA is an omega-3 fatty acid derived from the essential fatty acid precursor α -linolenic acid. Humans should obtain DHA from their diets, either as DHA itself, its precursor α -linolenic acid, or the intermediates in the biosynthesis of DHA such as eicosapentaenoic acid (EPA). The level of DHA in the brain fluctuates with the amount of dietary intake and the stage of life [55]. DHA accumulates rapidly in the grey matter of the cortex in the late prenatal and early postnatal period when the growth in volume is the greatest, and declines progressively during the aging process when there is a reduction in cortical volume [56]. Evidence suggests that DHA deficiency is associated with cognitive and behavioural deficits [55]. A high rate of autism is found in infants who are born prematurely or who have low birth weight [57]. Given that the rate of DHA accumulation is the greatest during the third trimester of pregnancy, this may indicate a link between DHA deficiency and autism [58].

Vitamin A

Vitamin A is especially needed for cell growth and differentiation, especially in epithelial tissues of the gut and brain. Studies by Megson reported that on 60 children who received natural vitamin A from cod liver oil [CLO] for three months or longer [59]. Some cases exhibited marked improvement within days; autism symptoms, such as language, eye contact, ability to socialize and sleep patterns, were consistently improved.

Although cod liver oil is unlikely to provide a sufficiently high content of omega-3 fatty acids to correct the extent of deficiency in developmentally impaired children, and the possibility of vitamin A toxicity limits its upper dosing level, it still has good clinical value. It is important to avoid CLO contaminated with mercury and other heavy metals [60, 61].

Vitamin D

Vitamin D hormone plays a major role in autism. Vitamin D is a fat-soluble vitamin which is converted to its biologically active form 1,25-dihydroxyvitamin D (calcitriol), a steroid hormone that regulates the expression of >900 different genes for brain development and function [62.] Vitamin D is first converted to 25(OH)D₃, which is the major stable circulating form of vitamin D. 25(OH)D₃ then is converted to the active vitamin D hormone, 1,25-dihydroxyvitamin D [63, 64]. The serum concentrations of 25(OH)D₃ required to maintain bone health is <30 ng/ml [65].

The incidence of autism has also been linked to maternal insufficiency of vitamin D in dark-skinned mothers living in northern latitudes [66]. In addition, Somali mothers who moved to Stockholm have been shown to be severely vitamin D deficient (< 20 ng/ml) and have approximately a 4.5 times higher risk of having a child with autism, as compared with native Swedes [67]. Vitamin D regulate the synthesis and response to oxytocin, as well as the response to vasopressin, which could help improve social functioning in ASD [68].

CONCLUSION:

Vitamin/mineral supplementation is beneficial in improving the nutritional and metabolic status of children with autism, and in reducing their symptoms. Based on the current findings, vitamin/mineral supplementation should be considered as an adjunct therapy for most children and adults with autism.

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