

REVIEW ARTICLE

Vitamin D and Autism Spectrum Disorder: A Review

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ABSTRACT

Recently, vitamin D has been shown to play important roles in the body, beyond its role in bone metabolism, including the regulation of immune and hormonal responses, antioxidant activity, proliferation, and cellular differentiation, and also has a critical role in brain development. Vitamin D deficiency is related to increased risk of neurodevelopmental disorders such as Autism Spectrum Disorder (ASD). Although the mechanisms are not fully understood, it seems that there is a relationship between low levels of vitamin D and the risk of Autism Spectrum Disorder. However, to prove this association, prospective Cohort and clinical trial studies with a large sample size are required. In this review, we explored the association between vitamin D and Autism Spectrum Disorder.

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Introduction

Vitamin D and Its Metabolism

Vitamin D is a steroid hormone that is provided from food sources or through exposure to sunlight (1), however, the diets consumed by most humans contain small amounts of vitamin D, unless it is rich in fatty fish. This vitamin is usually made from 7-dehydro-cholesterol in the skin through UVB radiation. Whether the vitamin D enters the body through dietary intake or through dermal synthesis, it is converted to 25-hydroxy cholecalciferol by the 25 α -hydroxylase enzyme in the liver and then is activated to 1,25-dihydroxy cholecalciferol by the enzyme 1 α -hydroxylase in the kidneys (2). More than 85% of vitamin D in the circulation is tightly bound to vitamin D binding protein (DBP), and only free form and the fraction bound to albumin, are active biological forms (3).

Serum levels of 25(OH)D is the best indicator

for vitamin D status determination (4). Regardless of age and sex, vitamin D deficiency has been reported worldwide, and according to global estimates, more than one billion people worldwide suffer from vitamin D deficiency (5). In addition to calcium/phosphorus and bone metabolism, vitamin D plays role in regulation of immune and hormonal responses, metabolic processes, antioxidant activity, cellular proliferation and differentiation, and also has a critical role in brain development. Vitamin D has effects on neurotrophic and neuroprotective processes in the brain, and also potentially affects neurotransmitters and synaptic plasticity (1, 6-11).

Vitamin D deficiency may lead to disturbances in the nervous system function and possibly increases the incidence of neurological diseases such as Autism Spectrum Disorder (ASD). Vitamin D appears to have the strongest effect on the nervous system in the perinatal period. It is also associated with changes

in the mental status of adults (1, 6-11), so that its deficiency has been reported in neurological diseases such as ASD, depression, multiple sclerosis (MS), Alzheimer's disease, Parkinson disease and attention deficit hyperactivity disorder (ADHD) (1).

Autism Spectrum Disorder (ASD)

Autism Spectrum Disorder consists of a wide range of neurodegenerative disorders, which originates from prenatal time and can be diagnosed in early childhood (12, 13). ASD is presented as problems in social skills, sensory issues and verbal and nonverbal communication, cognitive deficits, learning problems and repetitive behaviors, as well as unique abilities (1, 4, 6). ASD is defined by behavioral symptoms (14), but little is known about the etiology (15) and there is no consensus about the cause of the disease, possibly interactions between genes (14) or unknown environmental factors, such as those related to autoimmunity (16-19), pre and postpartum infections (20), exposure to thalidomide, valproic acid or alcohol during pregnancy (21-23), and also higher maternal and paternal age plays role in the etiology (24). Generally, ASD risk factors include genetic and environmental factors (4). ASD is associated with more than 440 different genes, although in approximately 70% of cases, the occurrence of this disorder is not directly related to genetics (1). Ecological studies have found an association between the number of ASD cases and environmental factors such as latitude, birth season, climate and also maternal skin type and vitamin D status (6, 25).

ASD is currently a common disorder. The prevalence of autism has increased by 700% since 1970 (26). The actual prevalence of ASD based on the CDC data is 1:68 and its prevalence in both boys and girls is 1:42 and 1:189, respectively (1, 6).

The current diagnosis of ASD is based on questionnaires that are usually completed by the parents or the health care providers. So far, no laboratory or biological indicators have been found to prove autism. Even no genetic test can indicate autism (1). Autism is not even diagnosed with physical characteristics. The average age of newly diagnosed patients is 4.5 years, but experts believe that the first signs of the disease appear at the age of 12 months and that the screening test can be done between 16 and 18 months old. An early and accurate diagnosis leads to faster intervention and better prognosis (1).

Vitamin D and Autism Spectrum Disorder

Different hypotheses have been proposed for the relationship between vitamin D and autism. Several studies have shown that in children with ASD, serum levels of vitamin D are lower than normal

(2, 4, 14). In 2012, Gehan et al. found lower serum levels of vitamin D in children with autism (mean serum levels of 15 ng/ml in children with autism compared to 30 ng/ml in healthy children), and also a significant association between serum vitamin D level and severity of ASD grading was reported (27).

It is not clear whether children with ASD are born with low levels of vitamin D (28), or limited exposure to sunshine leads to lower levels of vitamin D in ASD patients. If the former is the case, and children with ASD are born with lower levels of vitamin D, then it's possible that vitamin D is a genetic-environmental factor in ASD children. There are studies suggesting that low levels of vitamin D in children with ASD has a genetic basis (14). Kocovska et al. found that children with ASD have significantly lower levels of vitamin D compared to their siblings whom all live in an environment with low sun shine (29). Also, Fernell et al. analyzed 58 pairs of siblings, one of them with ASD and the other was healthy, and concluded that the serum levels of vitamin D at the birth time were lower in children with ASD (13). Schmidt et al. investigated the relationship between ASD and common vitamin D polymorphisms in CHARGE Cohort and found that polymorphisms related to lower levels of vitamin D, were more common in children with ASD (30).

Different views about the disease have suggested that oxidative stress is a possible cause of ASD. In autism, markers of oxidative stress are increased, while the level of glutathione, one of the most important antioxidants in the body, decreased (31). It has been shown that vitamin D is important in regulating the production of antioxidants such as glutathione, superoxide dismutase and thioredoxin reductase (1, 32). Therefore, it can exert protective effects against ASD.

On the other hand, it has been shown that in patients with ASD, plasma oxytocin level and serotonin concentration in the brain and blood-brain barrier were low (4, 33, 34). Oxytocin and serotonin are involved in modulating the social behaviors, and it has been shown that *vitamin D response elements* are present in the genes involved in the synthesis of serotonin and oxytocin. So, in this way, vitamin D can play a role in modulating social behaviors (4).

Vitamin D and ASD-Mechanism

The biological active form of vitamin D, $1,25(\text{OH})_2\text{D}$, inhibits synthesis of inducible nitric oxide synthase, which catalyzes nitric oxide, a free radical that can damage cells. Furthermore, $1,25(\text{OH})_2\text{D}$ stimulates gamma-glutamyl transpeptidase activity, which causes the production of glutamine, an antioxidant that destroys free radicals (1).

Vitamin D also stimulates brain cells to produce

a number of growth factors such as nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and neurotrophin-3 (NT3). Regarding neurotrophic and neuroprotective activities of vitamin D, it is suggested that this vitamin can stimulate neuronal growth, so vitamin D is likely to slow down the progression of neurodegenerative diseases (1).

Three possible implications of vitamin D in ASD have been indicated including (i) Vitamin D is associated with DNA repair genes and it repairs mutated genes in individuals, thereby reducing the risk of ASD (35), (ii) Vitamin D plays an important role in the immune system. There is evidence of neuroglial activity and neuroinflammation in the brain of patients with ASD. Vitamin D is important in regulating the production of antioxidants such as glutathione, superoxide dismutase, and thioredoxin reductase. Therefore, considering the role of vitamin D in regulating the production of antioxidants, vitamin D can reduce the activity of neuroglial cells and reduce neuroinflammation (32, 36), and (iii) There are reports of autoimmune conditions in people with ASD, which includes the presence of maternal antibodies in the brain tissue of the fetus (37). Vitamin D plays an important role in inducing T regulatory cells that these cells regulate the control of antibodies associated with auto-immune. Therefore, vitamin D induces T regulatory cells to reduce the the risk of auto-immunity and protect the fetus (11, 38).

Three different independent findings point towards a role for vitamin D in the development of ASD including (1) Increasing the risk of ASD in migrant children, especially from countries where their populations have darker skin color, as well as cultures in which women use covering clothing and do not benefit from other ways to take vitamin D, (2) Low levels of 25(OH)D in newborns who later got advanced ASD, as well as in children and adults with ASD, and (3) The relationship between the season and the ASD (13).

Vitamin D and ASD-Latitude and Season

Latitude and sunlight exposure affect the prevalence of ASD in different societies, with a higher prevalence of ASD in higher latitudes and in those who have less exposure to sunlight (4). Cannell et al. (2008) observed a higher incidence of ASD in areas with limited sunshine due to higher latitude or cloud coverage (28). Also, the results of an ecological study revealed that the prevalence of ASD among people aged 6-17 years had a significant negative correlation with the dose of UVB (39).

On the other hand, sunlight exposure and seasons affects the status of patients with ASD. As observed, the depletion of body vitamin D at the end of winter

and early spring, due to limited sunshine, is likely to aggravate ASD symptoms and increases the behavioral problems (4). Also, in adults with severe ASD who lived in a community center in Italy, behavioral problems increased dramatically in the spring and decreased in the fall (40).

Vitamin D and ASD- Supplementation

High doses of vitamin D have a therapeutic effect on ASD (14). Saad et al. treated ASD children aged 3 to 9 years, with 300 IU/Kg/day vitamin D for 3 months, and concluded that 80% of the participants had a significant improvement in the childhood autism rating scale (CARS). They also pointed that vitamin D was cheap, available, and safe. In addition, it might have a beneficial effect on patients with ASD, especially when its serum level is above 40 ng/ml (41). Also, in a case report, treating a 36-month-old child with ASD and rickets, with 150,000 IU/month of vitamin D for 2 months resulted in 3 degrees of improvement in the ASD standard ranking (42). Studies in this area are limited and further studies are needed to provide suggestions.

Vitamin D and ASD-Pregnancy

Vitamin D plays an important role in brain development during pregnancy (14). Its deficiency is associated with preeclampsia, premature birth, small for date, and gestational diabetes during pregnancy. Also, vitamin D deficiency during pregnancy is likely to be associated with ASD (14). In a study in Australia, the concentration of vitamin D less than 49 nmol/L in the 18th week of gestation was significantly associated with an increased risk of ASD in children (1). However, the desirable and optimal dose of vitamin D, as well as its proper levels, has not yet been detected (6). Stubbs et al. in 2016 prescribed 5000 IU/day vitamin D for pregnant mothers who already had a child with ASD. Newborns were also given 1000 IU/day vitamin D for three years. They followed the children for 3 years and gained promising results, and the risk of autism decreased from 20% to 5%. However, the sample size of this study was very small and there was no control group in this study (14). In another study, there was a positive correlation between vitamin D deficiency in mother and the risk of ASD in children. But in this study, the sample size was small and pre-recorded data were also used (15). Fernell et al. suggested that low levels of maternal vitamin D are likely to be a risk factor for ASD. They achieved these results by examining the levels of vitamin D in newborns who later developed advanced ASD. But these results require confirmation with larger sample sizes (13). In countries with higher latitudes, such as Sweden, children of mothers with darker skin color were at higher risk of

ASD with mental disability. Higher level of melanin in dark skins of these people, reduces the absorption of UVB by the skin, which reduces the levels of vitamin D in these individuals (43). A number of studies in Sweden, Denmark, UK, and the Northeastern USA have shown that most children with ASD are born in the winter and spring, with the highest rate in March, and suggest that lower levels of vitamin D in mothers, during pregnancy, is probably a risk factor (13) because the development of the embryo's brain occurs at the end stage of the pregnancy, so vitamin D in this period can have an effect on the brain's growth of the fetus (25).

Conclusion

Overall, it seems that there is a relationship between low levels of vitamin D and the risk of ASD, but to prove this, prospective cohort studies and clinical trials with large sample sizes are needed.

Conflict of Interest

None declared.

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