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Vitamin D Status and Its Association with Attention Deficit Hyperactivity Disorder (ADHD) in Children

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Vitamin D is a potent central nervous system (CNS) agent. Different parts of CNS, especially hypothalamus and substantia nigra are targeted by vitamin D. Vitamin D can affect production of neurotrophin agents and neurotransmitters. It can also prevent oxidative stress in neurons. Several diseases such as schizophrenia and multiple sclerosis might be associated with vitamin D deficiency (Wrzosek *et al.*, 2013). Based on previous studies, a low vitamin D3 level was associated with attention deficit hyperactivity disorder (ADHD) (Bener and Kamal, 2013, Goksugur *et al.*, 2014, Shang-Guan and Zhao, 2015). This disorder is a neuropsychiatric disease with a high prevalence among children. Boys constitute a large group of patients while girls show more intensive symptoms. Classic symptoms of ADHD include inattention, hyperactivity, and aggression. Overall prevalence of ADHD is 5.29% among children (Sadock BJ, 2009). This disorder can impose a significant economic and health burden on societies (Doshi *et al.*, 2012). Thus, the aim of this review was to overview the role of vitamin D in treating ADHD.

The association between vitamin D and ADHD: These findings comprise case-control, cross-sectional, and cohort studies.

Case-control studies: Bener et al. conducted a large case-control study on 1331 cases and 1331 healthy controls aged 5 to 18 years from June 2011 to May 2013. Serum 25-OH-vitamin D, calcium, phosphorus, albumin, billirubin, calcium, magnesium, urea, cholesterol, triglyceride, as well as socio-demographic and medical data were collected. This study indicated a significant vitamin D deficiency among children with ADHD. Furthermore, they had been exposed to sunlight less than the healthy children and had lower serum calcium level (Bener and Kamal, 2013). Goksugur

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et al. in a case-control study on 60 ADHD children and 30 healthy controls aged 7-18 years, demonstrated a relationship between low 25-OH-vitamin D and ADHD (Goksugur *et al.*, 2014). Another study by shang-Guan et al. on 97 children with ADHD and 97 healthy matched control showed that lower 25-OH-vitamin D levels may contribute to ADHD (Shang-Guan and Zhao, 2015). Gustafsson et al. conducted a study on 202 newborn children later diagnosed with ADHD and 202 healthy matched controls to investigate vitamin D3 status in newborn children with ADHD. Umbilical cord blood samples were collected to measure 25-OH-vitamin D levels, but no significant association was observed that might be due to weak statistical power of the study (Gustafsson *et al.*, 2015). Sharif et al. carried out a study on 37 children with diagnosed ADHD and 37 healthy controls. They observed lower serum vitamin D levels in children with ADHD compared to healthy controls (Sharif *et al.*, 2015). Avcil et al. investigated 105 children with ADHD and 95 healthy age and gender matched controls. In this regard, 25-OH-vitamin D, calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase (ALP) were measured in venous blood samples. The results showed that vitamin D deficiency is correlated with ADHD. Furthermore, a blunted PTH response and impaired calcium homeostasis were observed among children with ADHD (Avcil *et al.*, 2017). Garipardic et al. designed a case-control study on 36 patients with ADHD, 18 patients with autism spectrum disorders (ASD), and 25 healthy age and gender matched controls aged 2-18 years. Mean platelet volume (MPV), serum vitamin D, and vitamin B12 levels were measured. The findings of this study demonstrated vitamin D and vitamin B12 deficiency among patients as well as an inverse association between both vitamins and MPV (Garipardic *et al.*, 2017).

Cross-sectional studies: Results from the nationwide German health interview and examination survey for children and adolescents (KiGGS) represented an inverse association among serum vitamin D levels, systolic blood pressure, and ADHD. In a cohort study on 6922 participants (11-17 years), three subgroups including 430 ADHD confirmed patients, 399 ADHD suspected patients, and 6492 controls were selected. A higher arterial blood pressure was observed in controls. In addition, an inverse association was found between blood pressure and vitamin D level in both ADHD groups. The results demonstrated that lower systolic blood pressure in children with ADHD and suspected children was mediated by vitamin D (Meyer *et al.*, 2017).

Cohort studies: In a birth cohort study on 1233 infants (mean age 2.7 ± 0.6 years) and by using a child behavior checklist for ages 1.5-5, it was revealed that there is an inverse relationship between cord 25-OH-vitamin D and ADHD symptoms among toddlers (Mossin *et al.*, 2016).

Most of these observational studies indicated vitamin D deficiency among patients with ADHD although most of them have some weaknesses in methodology (e.g., small sample size or weak statistical power). Moreover, the observational data which can improve the causal association are still lacking.

The effect of vitamin D on ADHD symptoms (clinical trials): To the best of authors' knowledge, there is only one vitamin D interventional study on children with ADHD. In this study 62 children with ADHD were enrolled based on DSM-IV criteria. Children were then randomly allocated into two groups. Vitamin D (2000 IU/day) or placebo along with standard treatment (methylphenidate) were administered for 8 weeks. Serum 25-OH-vitamin D levels were measured at the baseline and after 8 weeks. Three standard questionnaires including ADHD rating scale-IV (ADHD-RS), Conner's Parent Rating Scale-Revised (CPRS-R), and Weekly Parent Ratings of Evening and Morning Behavior (WPREMB) were used. The questionnaires were aimed to evaluate the symptoms at the baseline, week 4, and end of the trial. After 8 weeks, serum levels of vitamin D and evening symptoms significantly improved in the intervention group (Mohammadpour *et al.*, 2016). Short period of

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intervention, low dose of vitamin D, and small sample size were the most considerable methodological deficits of this study.

Due to the strong enough evidences on vitamin D deficiency and its association with ADHD prevalence and also lack of enough longitudinal and interventional studies dealing with the causal association between vitamin D and ADHD, it is highly recommended to conduct such studies in future.

Authors' contribution

Hemamy M., and Askari G. designed the work. Hemamy M. wrote the manuscript. Hemamy M., revised the manuscript and two authors approved the final version of the manuscript. There is also a consensus between two authors for all aspects of the work.

Conflict of interest

The authors declare no conflict of interest.

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