

Effect of Vitamin D and Magnesium Supplementation on Behavior Problems in Children with Attention-Deficit Hyperactivity Disorder

Abstract

Background: Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by the three main symptom domains including inattention, hyperactivity, and impulsivity. Recent findings suggested that nutrients might play an important role in the pathology of ADHD. The present study aimed to examine the effects of Vitamin D and magnesium supplementation on behavior problems in children with ADHD. **Methods:** This double-blind, randomized controlled clinical trial study was conducted on 66 children with ADHD in Clinic of Noor and Ali Asghar Hospital in Isfahan, Iran, in 2016. Children were randomly allocated to receive both Vitamin D (50,000 IU/week) and magnesium (6 mg/kg/day) supplements ($n = 33$) or placebos ($n = 33$) for 8 weeks. Conners' Parent Rating Scale was used to evaluate children's behavior at baseline and at the end of the study. **Results:** After 8 weeks of Vitamin D consumption as well as magnesium, the serum levels of 25-hydroxy-Vitamin D3 and magnesium increased significantly in the intervention group compared with placebo group. Supplementation with Vitamin D and magnesium caused a significant decrease in conduct problems, social problems, and anxiety/shy scores; but it had no significant effect on psychosomatic problems score. **Conclusions:** Vitamin D and magnesium supplementation in children with ADHD was effective on conduct problems, social problems, and anxiety/shy scores compared with placebo intake, but it did not affect psychosomatic problem scores, significantly.

Keywords: Attention-deficit disorder with hyperactivity, magnesium, randomized clinical trial, Vitamin D

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a serious neurodevelopmental condition characterized by the three main symptom domains including inattention, hyperactivity, and impulsivity.^[1] The estimated prevalence of ADHD is between 5% and 7% in schoolchildren worldwide.^[2,3] In Iran, its prevalence is 5.03% among boys and 2.79% among girls.^[4] ADHD impairs school functioning and academic achievement profoundly.^[5] It is revealed that IQ in children with ADHD is lower than their peer.^[6,7] Furthermore, learning disorders (LDs) are more common in youth with ADHD.^[8] Lower IQ and LD accompanied by ADHD symptoms are major reasons for academic underachievement.^[6-8] These impairments can affect children's quality of life and impose substantial costs on their family, health-care services, and educational systems worldwide.^[5,9]

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ADHD is a complex disorder influenced by genetic and environmental factors.^[10] Prenatal exposures such as maternal smoking, psychosocial and dietary factors are some of these environmental factors.^[10,11] Recent findings suggested that nutrients might play an important role in the pathology of ADHD.^[12,13] Moreover, some studies showed that there were associations between nutrient levels and ADHD behaviors.^[14] Based on recent studies, magnesium and Vitamin D levels might contribute to symptomatology of ADHD.^[15-17]

Magnesium is an essential element to maintain the body performance.^[18] Many observational studies showed that the serum magnesium level in ADHD children was lower than controls.^[19-21] There are few interventional studies that assay the effect of magnesium intake on ADHD-related outcomes.^[15] Magnesium-B6 supplementation in children with ADHD resulted in a significant improvement in ADHD symptoms.^[22-24] Magnesium supplementation

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in combination with polyunsaturated fatty acids and zinc decreased inattention, hyperactivity, and impulsivity in children with ADHD.^[25] Magnesium supplementation along with standard treatment improved inattention, hyperactivity, impulsivity, opposition, and conceptual level in children with ADHD.^[26,27]

Vitamin D is a fat-soluble vitamin which is necessary for calcium metabolism, growth, and development of musculoskeletal system and prevention of many chronic diseases.^[28]

Recently, it has been shown that Vitamin D deficiency is more prevalent in children with ADHD compared to healthy children.^[16,17] To the best of our knowledge, there is only one interventional study that examines the effect of Vitamin D supplementation on ADHD in children.^[29] In this study, Vitamin D supplementation caused a significant improvement in ADHD evening symptoms.

Recent studies suggest possible interactions between Vitamin D and magnesium.^[30-34] Vitamin D supplementation could elevate serum magnesium levels.^[30,31] Furthermore, serum levels of Vitamin D might be affected by magnesium intake.^[32] In addition, magnesium might affect Vitamin D metabolism.^[33,34]

Therefore, the aim of the present study is to determine the effect of Vitamin D and magnesium supplementation on behavior problems in children with ADHD.

Methods

This double-blind, randomized controlled clinical trial study was conducted on 74 children with ADHD (22 girls and 52 boys) in Clinic of Noor and Ali Asghar Hospital in Isfahan, Iran, from March 10 to May 22, 2016. Samples were calculated with a confidence interval of 95% and 80% power of the test ($S = 24$, $d = 8.2$). The study was approved by Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran. This trial was registered at Iranian Registry of Clinical Trials as IRCT2016030326886N1.

The inclusion criteria were: (1) ADHD diagnosis using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV): DSM IV diagnoses ADHD based on ADHD-related symptoms. A minimum of six out of nine symptoms of inattention and a minimum of six out of nine symptoms of hyperactivity/impulsivity in two or more settings (e.g., home and school) is associated with ADHD diagnosis;^[1] (2) age between 6 and 12 years old; (3) signing informed written consents by children's parents to participate their children in the study; (4) the serum 25-hydroxy-Vitamin D (25-OH-Vitamin D) level <30 ng/dl;^[35] and (5) the serum Mg <2.3 mg/dl.^[36] The exclusion criterion was: Having any other diseases, for example, comorbid psychiatric disorders like autism spectrum disorders (ASD).

Despite our recommendation, not to use multivitamin-multimineral supplements, eight children had consumed multivitamins with Vitamin D. Therefore, they were excluded from the study before random allocation. Participants ($n = 66$) randomly allocated to either a supplement group ($n = 33$) or a placebo group ($n = 33$) using block randomization after stratification for sex. The block size was two and concealed from the executor. An independent person made random allocation cards using computer-generated sequence and used sequentially numbered, sealed, opaque envelopes to conceal the allocation. Neither the researcher nor the participants were aware of the two allocated groups. Children in supplement group received Vitamin D (50,000 IU/week) in the form of oral pearls and magnesium (6 mg/kg/day)^[18] in the form of oral tablets. Children in placebo group received Vitamin D (edible paraffin oil) and magnesium (microcrystalline cellulose and stearic acid) placebos which were similar in appearance, color, and taste to these supplements and produced in the School of Pharmacy, Isfahan University of Medical Sciences. The follow-up period lasted eight weeks. Supplements were given to the participants by an independent person in the recruitment center. Both groups received drug medication (Ritalin). Participant's compliance was measured through compare the serum levels of Vitamin D and magnesium before and after the supplementation in two groups.^[37]

Detailed information about sex, age, and taking medications was collected by a checklist.

Anthropometric measurements

Height was measured in a standing position, without shoes and by a tape measure with a precision of 0.5 cm. Weight was determined with minimal clothing, without shoes and by analog scale with a precision of 100 g. Body mass index (BMI) was calculated by weight in kilograms divided by height in meters squared.

Assessment of behavior problems

Children's behavior problems (conduct problems, social problems, anxiety/shy, and psychosomatic problems) were scored and evaluated using the Conners' Parent Rating Scale-48 (CPRS-48). This questionnaire is a 4-point Likert scale (not at all = 0, just a little = 1, pretty much = 2, and very much = 3) which includes 48 questions to evaluate the symptoms.^[38] This scale has been validated in Iran.^[39] CPRS-48 questionnaire was filled by children's parents at baseline and at the end of the trial period.

Biochemical measurement

Serum levels of 25-OH-Vitamin D and magnesium were measured at baseline and at the end of the trial period. Serum levels of 25-OH-Vitamin D were measured by enzyme-linked immunosorbent assay (ELISA) method with a commercially available ELISA kit from Immundiagnostik AG, Bensheim, Germany. Serum 25-OH-Vitamin D levels

were categorized as: deficient (serum levels <10 ng/ml); insufficient (serum levels between 10 and 30 ng/ml); and sufficient (serum levels >30 ng/ml).

Serum levels of magnesium were measured by an autoanalyzer (Hitachi 917, Roche Diagnostics® GmbH, Mannheim, Germany) using a commercially available kit.

Statistical analysis

Normality of variables distribution was assessed by Kolmogorov–Smirnov test. As the outcome variables were not normally distributed, we used nonparametric tests. The Wilcoxon signed-rank test was used for comparing intragroup changes. The Mann-Whitney test was used for comparing intergroup changes. Chi-square test was used to assess the significance level of qualitative variables include gender and BMI between the two groups. Participant's compliance was measured through the comparison of the mean changes in serum levels of 25-OH-Vitamin D and magnesium in the intervention group with the placebo group during the study. For all analyses, SPSS 19 (SPSS, Inc., Chicago, IL, USA) was used. $P = 0.05$ considered as significance level.

Results

Among 74 children with ADHD, eight children were excluded from the study due to consuming multivitamins with Vitamin D before randomization. None of the participants lost to follow-up; therefore, 66 participants completed the study and were included in the final analysis [Figure 1].

Mean values for age, sex, BMI, and other general characteristics of participants represented in Table 1. No significant difference was found in terms of age, sex, BMI, and Ritalin dosage between intervention and placebo groups. Baseline characteristics of conduct problems, social problems, psychosomatic problems, and anxiety/shy scores were not significant in the two groups [Table 2]. Furthermore, there were not any significant differences between the serum levels of 25-OH-vitamin D and magnesium at baseline in the two groups [Figures 2 and 3].

After 8 weeks, the serum 25-OH-Vitamin D level increased significantly in the intervention group compared with the placebo group (28.71 ± 10.06 vs. 0.07 ± 1.59 ; $P = 0.001$). Furthermore, the serum magnesium level increased in the intervention group compared with the placebo group (0.24 ± 0.1 vs. 0.006 ± 0.03 ; $P = 0.001$), significantly [Figures 2 and 3]. Serum 25-OH-Vitamin D and magnesium levels were changed significantly in the intervention group ($P = 0.001$). However, there were not any significant changes in placebo group.

Supplementation with Vitamin D and magnesium caused a significant decrease in conduct problems score (-3.30 ± 0.51 vs. 0.24 ± 0.16 ; $P = 0.001$), social problems score (-2.21 ± 0.51 vs. 0.18 ± 0.19 ; $P = 0.001$), and anxiety/shy score (-1.42 ± 0.25 vs.

0.03 ± 0.06 ; $P = 0.001$) in intervention group compared with placebos. However, supplementation had no significant effect on psychosomatic problems score (-0.24 ± 0.16 vs. 0.03 ± 0.06 ; $P = 0.20$) [Table 2].

According to Table 1, there were not any significant differences between intervention and placebo group for age, BMI, and Ritalin dose. In addition, we assessed the correlation of these confounders with outcome variables, and we did not find any significant correlation. Thus, we did not consider these variables as confounder. Sex was matched during the study. All children were monitored for clinical and laboratory evidence of toxicity or other adverse

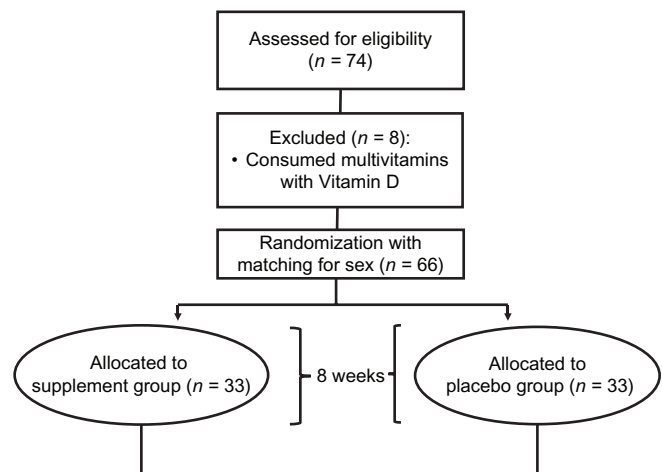


Figure 1: Participants' flow diagram

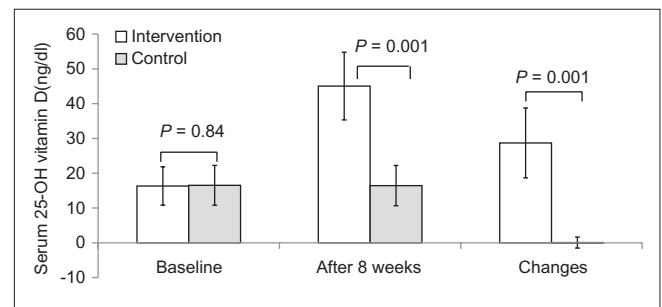


Figure 2: Serum 25-hydroxy-Vitamin D levels of participants at study baseline and end of trial. P values obtained from Mann-Whitney test. P value for comparison of changes between the two groups was 0.001

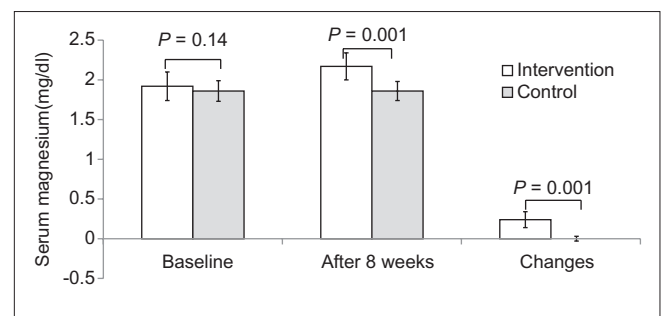


Figure 3: Serum magnesium levels of participants at study baseline and end of trial. P values obtained from Mann-Whitney test. P value for comparison of changes between the two groups was 0.001

events. No adverse effects of Vitamin D and magnesium supplementation were reported at the end of this study.

Discussion

In the present study, supplementation with Vitamin D and magnesium in children with ADHD decreased conduct problems, social problems, and anxiety/shy scores compared with placebo intake, however, did not affect psychosomatic problems scores, significantly. To the best of our knowledge, this study is the first clinical trial to examine the effects of Vitamin D and magnesium supplementation on behavior problems in children with ADHD.

ADHD is the most clinically manifested neuropsychiatric condition which contains three diagnostic symptoms: Lack of attention, impulsivity, and hyperactivity. It is a complex disorder that is caused by genetic and environmental factors.^[40] Recently, it has been revealed that dietary factors (such as Vitamin D or magnesium) play an important role among environmental factors.^[16,40] Global

prevalence of ADHD is about 5% in children.^[1] ADHD has a high comorbidity with other psychiatric diseases such as ASD and LD.^[8,41] The economic costs, especially on education and health care of children with ADHD with or without comorbid conditions, are substantial.^[41,42]

To the best of our knowledge, except one adjunctive therapy,^[29] there are no other studies on the effect of Vitamin D as a treatment alone or in combination with other nutrients on the severity of symptoms in children with ADHD although low 25-OH-Vitamin D3 levels have been associated with ADHD in observational studies.^[16,17,29] Mohammadpour *et al.* conducted a randomized, double-blind placebo-controlled trial on 62 children with ADHD aged 5–12 years. They prescribed either 2000 IU Vitamin D or placebo per day in addition to methylphenidate for 8 weeks. Severity of symptoms was measured through CPRS-Revised(s), ADHD rating scale-IV, and Weekly Parent Ratings of Evening and Morning Behavior. Serum Vitamin D levels and ADHD evening symptoms improved significantly in the intervention group compared with the placebo group after 8 weeks. Small sample size, short duration of follow-up, and low doses of Vitamin D are limitations of this study.^[29] Furthermore, psychosomatic problems were not assessed in this study.

Vitamin D affects various brain functions directly through its nuclear receptors (Vitamin D receptor or VDR) scattered throughout the central nervous system. Experimental and *in vitro* studies revealed that Vitamin D involved in several pathways in the brain including synthesis of neurotrophic agents, regulation of numerous neurotransmitters, neuroprotection, and neuroimmunomodulation. In humans, cortex, cerebellum, and limbic system, the three important parts of the brain, are involved in the behavior and are targeted by VDR. Thus, VDR polymorphisms could lead to psychiatric conditions such as ADHD, depression, and anxiety.^[43,44]

We found only three interventional studies which used magnesium as a treatment and CPRS as an assessment tool in ADHD.^[23,26,27] Magnesium was used in combination with other nutrients or along with standard treatment in these studies. In

Table 1: General characteristics of the study participants^a

	Intervention (n=33)	Control (n=33)	P ^b
Age (years)	9.06±1.76	9.15±1.46	0.80
Weight (kg)	31.33±9.93	31.17±8.82	0.96
Height (cm)	129.46±11.12	129.34±9.48	0.87
BMI (kg/m ²), n (%)			
Underweight	3 (9.10)	1 (3.00)	0.66
Normal weight	17 (51.50)	21 (63.60)	
Overweight	8 (24.20)	7 (21.20)	
Obese	5 (15.20)	4 (12.10)	
Sex, n (%)			
Boy	23 (69.7)	23 (69.7)	0.99
Girl	10 (30.3)	10 (30.3)	
Ritalin dose (mg/kg)	31.33±9.93	31.21±8.81	0.93

^aData are presented as means±SD other than those specified, ^bFor comparison of numerical values Mann–Whitney test, and for qualitative values, Fisher’s exact test has been used. BMI=Body mass index, SD=Standard deviation

Table 2: The effect of Vitamin D and magnesium supplementation in children with attention-deficit hyperactivity disorder based on Conners’parent rating scale^a

Scales	Intervention (n=33)			Control (n=33)			P ^c	P ^d	P ^e
	Baseline	8 th week	Change ^b	Baseline	8 th week	Change ^b			
Conduct problems score	16.91±1.78	13.61±1.45	-3.30±0.51	17.24±1.62	17.48±1.56	0.24±0.16	0.69	0.05	0.001
Social problems score	10.24±1.08	8.03±0.96	-2.21±0.51	10.42±1.03	10.61±1.00	0.18±0.19	0.86	0.07	0.001
Psychosomatic problems score	8.79±0.90	8.55±0.84	-0.24±0.16	9.00±0.88	9.03±0.88	0.03±0.06	0.81	0.69	0.20
Anxiety-shy score	8.24±0.65	6.82±0.55	-1.42±0.25	8.06±0.61	8.09±0.60	0.03±0.06	0.86	0.09	0.001

^aReported values are means±SEM, ^bCalculated by subsidizing values at 8th week from values at baseline, ^cComparison of values at baseline between the two groups using Mann–Whitney test, ^dComparison of values at 8th week between the two groups using Mann–Whitney test, ^eComparison of values changes between the two groups using Mann–Whitney test, ^{c,d,e}The P=0.05 considered as significance level. SEM=Standard error of mean

addition, these studies had some limitations including very small sample size and lack of blinding. Moreover, none of these three studies were assessed our subscales such as psychosomatic problems in the present study.^[23,26,27]

Magnesium has an important role in regulating of various brain functions (e.g., behavior). Activity of numerous neurotransmitters such as dopamine, norepinephrine, and serotonin is dependent on magnesium. Furthermore, release of n-methyl-d-aspartate-induced norepinephrine is inhibited by magnesium.^[18] Thus, as it previously has been shown, magnesium might be useful as a therapeutic agent in the treatment of ADHD.^[22-27]

There is an association between serum magnesium and Vitamin D levels.^[45] Vitamin D supplementation could improve serum levels of magnesium.^[30,31] Similarly, magnesium intake might be associated with reduced risks of vitamin D deficiency and insufficiency.^[32] Besides, magnesium could affect vitamin D production. The synthesis of 24,25(OH) 2D3 and 1,25(OH) 2D3 might be modulated by magnesium *in vivo* and *in vitro*.^[33,34] Furthermore, Vitamin D and magnesium affect similar areas of the brain involved in behavior.^[18,43]

Our study had several limitations: First, this study did not have a 2 × 2 factorial design to assess the effect of either Vitamin D or magnesium supplementation on the study's variables, separately. Therefore, only the effect of combination of Vitamin D and magnesium supplements was evaluated. This could be due to our small sample size. In addition, dietary intakes of magnesium and Vitamin D were not assessed and duration of follow-up was short.

Conclusions

Vitamin D and magnesium supplementation in children with ADHD was effective on conduct problems, social problems, and anxiety/shy scores compared with placebo intake but did not affect psychosomatic problems scores, significantly.

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Conflicts of interest

There are no conflicts of interest.

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