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ORIGINAL ARTICLE

Effect of vitamin D treatment in children with attention-deficit hyperactivity disorder

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Abstract

Background In this research the symptom improvement of attention-deficit hyperactivity disorder (ADHD) of children was assessed by oral vitamin D administration in Tabriz, Iran.

Methods In this double-blind, randomized clinical trials, 96 children (2–18 years) were enrolled to placebo and vitamin D groups. Children took vitamin D pearl (50,000 IU/week) or placebo for 6 weeks. Children, who had the change in methylphenidate dosage and received any anticonvulsants and corticosteroids were excluded from the research. ADHD symptoms were diagnosed by Conners parent rating scale (CPRS) test at baseline and after intervention. ADHD Conners divided into inattention (IA), hyperactivity/impulsivity (H/I) and combination type (C) subscales. Vitamin D serum level was assessed at baseline and after 8 weeks in both groups.

Results The differences between CPRS and its subscales were not significant at baseline ($P > 0.05$). The Conners IA score was decreased in vitamin D group ($P < 0.05$; adjusted with age and baseline values). ADHD Conners and all subscale scores reduced remarkably after intervention in patients with insufficient level of vitamin D compared to placebo ($P < 0.05$).

Conclusions Oral vitamin D improved ADHD symptoms with a particular effect on inattention symptoms. In addition, symptoms related to all subscales were improved remarkably in patients with insufficient level of vitamin D. Vitamin D treatment in children with ADHD could be considered due to the expand benefit of vitamin D in body.

Keywords Attention-deficit hyperactivity disorder · Children · Conners parent rating scale · Vitamin D

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a behavioral disorder defined by the following symptoms such as inattention, hyperactivity, impulsivity and restlessness [1, 2]. The prevalence of ADHD in children is 5.3% [3]. ADHD affects ability of learning in children [4]. Different behavioral criteria categorized patients into hyperactivity/impulsivity (H/I), inattention (IA) and combination type (C) [5]. The exact pathophysiology of ADHD is not well identified [1, 2]. However, the role of the neurotransmitters such as dopamine and serotonin in attention, motivation, concentration and other cognitive functions is well known [6, 7]. In addition, previous studies demonstrated that ADHD children have abnormalities in dopaminergic system of basal ganglia [6].

The protective function of elements such as iron and zinc on control of ADHD symptoms had shown in previous study [8]. Vitamin D is a fat-soluble secosteroid, which has a major role in bone and calcium homeostasis. Vitamin D receptors are distributed across many tissues. The widespread distribution of vitamin D receptors on different tissues confirms the various potential physiologic actions of this vitamin in the body [9, 10]. Evidences showed that different psychiatric diseases such as autism and depression are related to vitamin D deficiency [8]. Studies have proposed a pathophysiological effect of low level of vitamin D

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in ADHD [6, 8, 11]. In addition, previous studies showed that vitamin D level is lower in ADHD children compared to normal children [6, 8, 11].

Furthermore, vitamin D may also have a neuroprotective effect by dopaminergic pathways [12]. It should be noted that vitamin D and its metabolites pass blood–brain barrier. Subsequently, it has the numerous effects on the central nervous system (CNS) [7].

Vitamin D deficiency prevalence in Iranian children is high [13]. We hypothesized that vitamin D supplementation would be effective in ADHD improvement. To the best of our knowledge, there is no published evidence about the effect of vitamin D supplementation on the improvement of ADHD symptoms yet. We aim to assess the effect of vitamin D supplementation on improvement of symptoms in ADHD children.

Methods

Study population

After institutional review board approval, the 2- to 18-year-old children (51 in vitamin D and 45 in placebo groups), who had confirmed diagnosis of ADHD, were assigned to this double-blind randomized clinical trial. All children were drawn from outpatient clinic of the child psychiatry department from March 2016 to April 2017 in Tabriz, Iran. All ADHD patients had stable symptoms and received methylphenidate before inclusion,which was continued with the same dose during the study. Patients with a history of any chronic disease, iron deficiency anemia, change of methylphenidate dosage, or received medications such as anticonvulsants, corticosteroids and any kind of vitamin supplements were excluded from the study.

All children were under supervision of pediatric psychiatrist. During the study, psychiatrist and patients were blinded about the group assignments (placebo or vitamin D). A local company manufactured both intervention and placebo pearls in a same shape and color. Both pearls contain Miglyol neutral oil. Intervention pearls had additional 50,000 IU vitamin D in each.

Intervention

Children were assigned into vitamin D and placebo groups via block randomization with four subjects in each block. All children in both groups were kept on methylphenidate consumption and no changes were made about their main treatment (dosage and medication). Vitamin D group received an oral supplement (pearl) of 50,000 IU vitamin D3 (cholecalciferol) per week for 6 weeks. Placebo of vitamin D was administered with a similar order in the placebo group. Blood samples were withdrawn from patients at baseline and after 6 weeks to assess the lab data. Demographic information, serum level of iron, total iron binding capacity (TIBC), calcium (Ca) and zinc were recorded at baseline for all patients. In addition, serum level of ferritin and 25-dihydroxy vitamin D (25-OH-D) were checked at baseline and after 8 weeks for both groups. Vitamin D level was measured based on serum 25-OH-D by enzyme-linked immunosorbent assay. In this study, the stages of serum vitamin D level were used according to approved levels as follows: vitamin D sufficiency: 20 to 100 ng/mL (50 to 250 nmol/L); vitamin D insufficiency: 12 to 20 ng/mL (30 to 50 nmol/L); vitamin D deficiency: < 12 ng/mL (< 30 nmol/L).

Measurement of ADHD severity

The Conners comprehensive behavior rating scale is a clinical tool which provides an overview of child behavioral disorders. The Conners rating scale is divided into three categories, which are determined by the person who filled it (parent, teacher and self-report). In this study the Conners parent rating scale (CPRS) was chosen. CPRS is a checklist which makes parental reports of the children's basic problems in the setting of outpatient psychiatry. The CPRS includes questions about different aspect of patients' problems and shows different type of ADHD symptoms [14]. Conners test demonstrates a severity and improvement of ADHD symptoms by numbers. The analysis of CPRS questions gives a total number as ADHD Conners number. In addition, all questions can be divided into three subscales by symptoms including inattention, hyperactivity/impulsivity and combination type. Additional numbers can be extracted for each subscale of ADHD (Conners IA, H/I and C) [14]. In addition, CPRS is validated in Persian language and used by routines with psychiatrist. In this study the CPRS was performed at baseline and after 8 weeks for all children in both groups under supervision of children psychiatrist.

Statistical analysis

Normal distribution was tested with the Kolmogorov–Smirnov test. Data with normal distributions were analyzed with independent *t* test. Continuous quantitative variables were expressed with mean ± standard deviation (SD). Categorical variables were described with frequency and percentage. The data were adjusted with confounding factors such as age and baseline ADHD Conners score with covariance analysis. Data were analyzed using SPSS version 21 and *P* values less than or equal to 0.05 were considered statistically significant.

Standard protocol approval, registration and patient consents

The research protocol of this study was approved by the local Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran, on February 2016. This clinical trial was attributed in the Iranian Registry of Clinical Trials (IRCT2017012826998N2). All patients and their parents were informed about the trial. Informed consent was obtained from all individual participants included in the study. Participants were free to keep on or quit the study at any time. The children in control group were treated with single dose of intramuscular injection of vitamin D 300,000 IU at the end of the study.

Results

Baseline characteristics

In this trial, 200 patients were assessed for eligibility. From all, 73 children did not meet the inclusion criteria and 25 declined to participate in this study. Finally, 102 children were randomized into two groups. Out of 102 subjects, 96 patients (51 in vitamin D and 45 in placebo groups), finished the study and included in analyses (Fig. 1). The differences between vitamin D and placebo groups in terms of gender and some biochemical parameters such as serum level of Ca, ferritine, Fe, TIBC and zinc were not significant at baseline as shown in Table 1. There is significant difference between ages at baseline in two groups ($P<0.05$).

Treatment response

During the study period, patients did not express any kind of side effects related to vitamin D supplementation. The difference between serum 25-OH-D level of groups was not statistically remarkable at baseline (Table 2). The frequencies of patients with sufficient, insufficient and deficient level of vitamin D at baseline were 37, 42.7 and 19.8%, respectively (Table 3). Serum 25-OH-D levels significantly elevated (mean increase 27.5 ng/mL) and achieved level of sufficiency after vitamin D administration in all patients in intervention group, while serum levels of vitamin D did not change significantly in placebo group.

The baseline CPRS and its subscale differences were not significant between two groups (Table 4). After 6-week supplementation, Conners ADHD, Conners IA and Conners H/I scores were reduced compared to baseline values ($P<0.05$) in vitamin D group, whereas Conners C scores reduction was not significant. The severity of ADHD Conners and its subscales changes were not statistically significant in placebo group compared to baseline values ($P>0.05$).

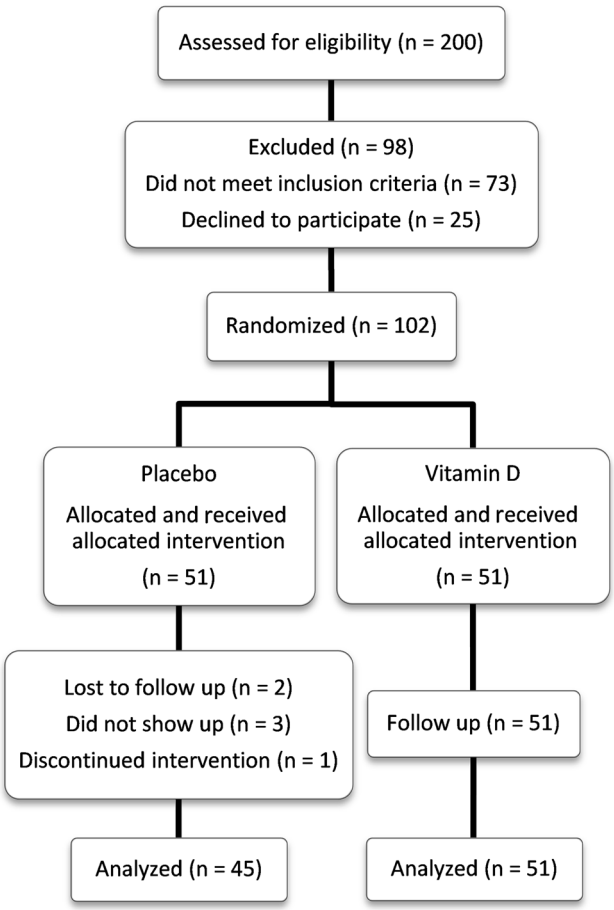

Fig. 1 Screening, randomization and follow-up of study participants

Between-groups comparison showed remarkable reduction in Conners IA score ($P<0.05$; adjusted with age and baseline values). Although scores of Conners ADHD, H/I and C reduced after supplementation in vitamin D group, there were no statistically significant changes compared to placebo group. Due to determine the role of baseline vitamin D status on Conners improvement after intervention, data analyzed and showed in Table 5. Between-groups analysis in Table 5 showed that ADHD Conners and all subscales scores of vitamin D group decreased significantly after supplementation in patients with insufficient level of vitamin D compared to placebo group (Table 5).

Discussion

The results indicated that 50,000 IU/week vitamin D supplementation decreased Conners ADHD and its subscales. However, this reduction is significant in Conners IA, which is related to inattention in children with insufficiency and deficiency of vitamin D. Furthermore, according to Table 5 Conners scores were improved considerably in patients with

Table 1 Comparison of baseline characteristics between the two groups

Variables	Vitamin D ($n=51$)	Placebo ($n=45$)	P value*
Age (y), mean ± SD	9.76 ± 2.38	8.58 ± 2.02	0.01
Gender, *n* (%)			0.17†
Male	45 (88.2)	35 (77.8)	
Female	6 (11.8)	10 (22.2)	
Mother age (y), mean ± SD	26.41 ± 5.38	27.24 ± 5.88	0.47
Ferritine (ng/mL), mean ± SD	41.66 ± 25.22	47.15 ± 21.98	0.26
Fe (mcg/dL), mean ± SD	89.85 ± 27.75	83.69 ± 34.41	0.54
TIBC (mcg/dL), mean ± SD	365.40 ± 64.32	349.71 ± 65.71	0.35
Calcium (mg/dL), mean ± SD	9.76 ± 0.45	9.74 ± 0.49	0.85
Zinc (mcg/mL), mean ± SD	90.42 ± 13.53	94.36 ± 17.86	0.27

Normal reference intervals; ferritine: 15–200 ng/mL; Fe: 50–170 mcg/dL; TIBC: 250–425 mcg/dL; calcium: 8.5–10.6 mg/dL; zinc: 0.60–1.20 mcg/mL. *TIBC* total iron binding capacity, *SD* standard deviation. *Independent sample *t* test, †Chi square test

Table 2 Comparison of 25(OH)D serum levels (ng/mL) at baseline and after 6 weeks in two groups

Group	Baseline	After 6 wk	MD[a], P†
Vitamin D	17.50 ± 6.98 17.9 (5.71–29)	44.98 ± 11.62 41.5 (30.1–82)	27.47 (24.87, 30.07), < 0.001*
Placebo	17.71 ± 6.01 18.3 (5.7–29.5)	14.84 ± 9.47 13.2 (5.2–65)	−2.87 (−5.40, −0.33), 0.027*
MD[b], P‡	−0.21 (−2.87, 2.44), 0.87	30.13 (25.80, 34.46), < 0.001*	

Data are mean ± standard deviation or median (min–max). *$P < 0.05$, †Paired *t* test, ‡Independent sample *t* test. [a, b]Mean difference (within group[a], between groups[b], 95% confidence interval)

Table 3 Vitamin D level stages frequency

Vitamin D level	Sufficient	Insufficient	Deficient
Baseline, *n* (%)			
Vitamin D	21 (41.2)	17 (33.3)	13 (25.5)
Placebo	15 (33.3)	24 (53.3)	6 (13.3)
After 6 wk, *n* (%)			
Vitamin D	51 (100)	0	0
Placebo	6 (13.3)	20 (44.4)	19 (42.2)

insufficient level of vitamin D. In line with our findings, 2000 IU/day vitamin D, with methylphenidate, improved evening symptoms of ADHD in children [7]. Different prevalence of deficient level of vitamin D in children with ADHD was reported [8, 11, 15–17]. Kamal et al. [11] showed lower levels of vitamin D in 5- to 18-year-old ADHD children compared to normal population. Morales et al. [18] showed the relation with maternal levels of vitamin D and ADHD symptoms in children four to 5 years. However, Strom et al. [19] did not demonstrate remarkable relation with vitamin D serum levels in 30th week of gestation and children ADHD symptoms in 22 years follow up. The major limitation of both cohorts is the lack of 25-OH-D levels assessment in patients [18, 19]. Moreover, Gustafsson et al. [20] showed that there is not any difference in intrauterine vitamin D level and ADHD development in later years compared to healthy controls. However, the study had weak statistical power to detect any association between ADHD and level of vitamin D. Association between deficient level of vitamin D and behavioral disorders were examined in many researches [21–23]. In adult rats, transient prenatal deficient level of vitamin D is related with hyperlocomotion [21]. Ubbenhorst et al. [22] reported that 1, 25-dihydroxy vitamin D levels in plasma were correlated with personality traits in adults. However, based on the cohort study in children, Tolppanen et al. [23] showed no relation between levels of vitamin D and behavioral problems. The main limitation of this study was using cases with limited behavioral problems [23]. Noorazar et al. [17] demonstrated U shaped relation between ADHD severity and vitamin D levels in children with ADHD.

There are some possible mechanisms for ADHD improvement by sufficient level of vitamin D. Vitamin D can effect nervous system through calcium transition [24] antioxidant properties [25], and also gene expression [26, 27]. Irregular dopamine concentration in specific regions of the CNS may play a role in ADHD etiology [12]. On the other hand, methylphenidate causes dopamine accumulation in synapses and progress attention, focus, and organized

Table 4 Comparison of ADHD conners and its subtypes at baseline and after 6 weeks in two groups

Variables	Vitamin D ($n=51$)	Placebo ($n=45$)	MD[b], P value
Conners ADHD			
Baseline	14.25 ± 7.17	14.77 ± 5.86	−0.52 (−3.20, 2.15), 0.69[†]
After 6 wk	11.92 ± 6.26	13.82 ± 6.22	−1.36 (−3.18, 0.45), 0.13[§]
MD[a]	2.33 (1.23, 3.43)	0.95 (−0.71, 2.62)	
P value[‡]	< 0.001	0.25	
Conners IA			
Baseline	10.31 ± 5.19	10.44 ± 4.26	−0.13 (−2.07, 1.80), 0.89[†]
After 6 wk	8.64 ± 4.04	10.44 ± 4.39	−1.65 (−2.98,−0.32), 0.01[*§]
MD[a]	1.66 (0.50, 2.82)	0.00 (−0.94, 0.94)	
P value[‡]	< 0.01[*]	1.00	
Conners H/I			
Baseline	6.00 ± 4.10	7.00 ± 3.90	−1.00 (−2.62, 0.62), 0.22[†]
After 6 wk	5.09 ± 3.92	6.33 ± 4.36	−0.21(−1.34, 0.90), 0.70[§]
MD[a]	0.90 (0.16, 1.63)	0.66 (−0.23, 1.56)	
P value[‡]	0.01[*]	0.14	
Conners C			
Baseline	6.00 ± 3.46	6.26 ± 3.29	−0.26 (−1.64, 1.10), 0.70[†]
After 6 wk	5.41 ± 3.14	5.97 ± 3.53	−0.31 (−1.26, 0.63), 0.51[§]
MD[a]	0.58 (−0.07, 1.25)	0.28 (−0.46, 1.04)	
P value[‡]	0.08	0.44	

ADHD attention-deficit hyperactivity disorder, *IA* inattention, *H/I* hyperactivity/impulsivity, *C* combination. [*]$P<0.05$, [†]Independent sample t test, [‡]Paired t test, [§]ANCOVA adjusted for age and baseline values. [a,b]Mean difference (within group[a], between group[b], 95% confidence interval)

Table 5 Comparison of the effects of intervention in Conners scores changes based on baseline status of vitamin D level in both groups

Vitamin D level (vitamin D/placebo)	Sufficient MD[a], P value[*]	Insufficient MD[a], P value[*]	Deficient MD[a], P value[*]
Conners ADHD			
Baseline	−0.29, 0.90	1.83, 0.36	−1.84, 0.59
After 6 wk	0.05, 0.97	4.73, 0.02	−1.91, 0.52
Conners IA			
Baseline	−1.59, 0.34	1.21, 0.42	0.38, 0.86
After 6 wk	0.83, 0.55	2.84, 0.05	0.21, 0.9
Conners H/I			
Baseline	2.39, 0.11	1.22, 0.26	−2.75, 0.22
After 6 wk	1.14, 0.41	2.93, 0.03	−3.12, 0.03
Conners C			
Baseline	−0.08, 0.94	1.43, 0.13	−2.53, 0.14
After 6 wk	−0.10, 0.92	2.13, 0.04	−2.29, 0.21

Data generated with independent sample t test. *ADHD* attention-deficit hyperactivity disorder, *IA* inattention, *H/I* hyperactivity/impulsivity, *C* combination. [*]$P<0.05$. [a]Mean difference (between groups)

thought [7]. Tekes et al. [28] showed that single dose of 0.05 mg vitamin D administration increases the dopamine level in brainstem and hypothalamus on neonatal rat brain. Furthermore, administration of calcitriol for 6 weeks in rats induced tyrosine hydroxylase (TH) expression [29]. TH is the enzyme responsible for catalyzing the conversion of tyrosine to dopamine in prefrontal cortex and hippocampus [30]. Moreover, Cui et al. [26] showed that vitamin D elevated TH expression in an in vitro study. In addition to above mentioned mechanism, vitamin D increases dopamine by glial cell line-derived neurotrophic factor (GDNF) expression stimulation [27]. GDNF plays an important role in differentiation and survival of dopaminergic neurons [30]. Defects in dopamine receptors, dopamine transporter-I (DAT-I) genes and polymorphism in D4 receptor lead to ADHD development [31, 32]. Peeyush et al. [33] confirmed that supplementation of vitamin D in diabetic rat modified increased expression of D2 receptors and downregulated D1 receptors to normal range. Release of dopamine from vesicle to synapse is inhibited by D1 and D2 receptors [33]. In another investigation, neonatal deficiency of vitamin D causes density improvement of dopamine transporters and increased affinity to dopamine in rats [34].

Another mechanism is antioxidant effect of vitamin D. Increased oxidative stress can be related to the pathophysiology of ADHD. Vitamin D improves the formation of glutathione, which has the antioxidant effects in brain [35]. Experimental studies reported that vitamin D deficiency facilitates oxidative stress response and changes multiple neuroendocrine transmitters [6].

Serotonin transporter promoter variation affects susceptibility to ADHD [36]. Vitamin D controls serotonin production by tryptophan hydroxylase 2 and tryptophan

hydroxylase 1. These two genes are responsible for the change of serotonin from tryptophan in the brain and other tissues [37].

Overall, adding vitamin D to methylphenidate resulted in remarkable improvements in the score of ADHD Conners related to inattention symptoms after 6 weeks within vitamin D group compared with placebo. Although the improvement of ADHD symptoms in patients with insufficient level was significant and more obvious compared to deficient level, it can be explained because of high number of patients in insufficient category (42.7 vs 19.8).

In conclusion, our research stated that adjunctive treatment of vitamin D may improve ADHD symptoms. Due to our results, the level assessment and treatment deficient and insufficient level of vitamin D in children with ADHD could be a promising method due to the numerous useful effect of vitamin D in body.

The limitation of this research is that, the numbers of allocated patients were small and single assessment tool (CPRS) was used for assessing outcomes. Duration of this study was 13 months and it affects sun exposure. In addition, the amount of sun exposure was not measured during the study. Additionally, methylphenidate consumption as a routine treatment protocol could mask the effects of vitamin D.

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Compliance with ethical standards

Ethical approval The research protocol of this study was approved by the local Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran, on February 2016. This clinical trial was attributed in the Iranian Registry of Clinical Trials (IRCT2017012826998N2). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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