European Journal of Integrative Medicine 25 (2019) 28–33

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Clinical trial

The effects of vitamin D supplementation on ADHD (Attention Deficit Hyperactivity Disorder) in 6–13 year-old students: A randomized, double-blind, placebo-controlled study

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ARTICLE INFO

Keywords:
Attention Deficit Hyperactivity Disorder
Supplementation
Students
Vitamin D
Randomized controlled trial

ABSTRACT

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is a common mental disorder in children. Drug treatment is the most prevalent method used to control it; however, considering the low efficacy and frequent side effects of current drugs, more attempts are needed to replace them with safer agents. Several studies have shown the beneficial role of micronutrients such as vitamin D in development and improving the performance of neuronal system. This research intended to study the effects of vitamin D supplementation in 6–13 year-old students with ADHD.

Methods: In this double-blind parallel clinical trial, the subjects were selected from among 6–13 year-old students with ADHD diagnosed by a child psychiatry specialist. Vitamin D3 supplements (1000 IU) or placebo given daily to 70 subjects for three months. ADHD symptoms were evaluated before and after the intervention using Conners Parent Questionnaire (CPQ), the Strengths and Difficulties Questionnaire Teacher Version (SDQT), the Strengths and Difficulties Questionnaire Parent Version (SDQP) and Continuous performances Test (CPT) scores.

Results: The mean scores of the CPQ, SDQP and SDQT showed a significant difference in the two groups after intervention ($p < 0.05$). The impulsivity mean scores of the CPT after intervention showed statistical significance ($p = 0.002$), but the attention ($p = 0.11$) and mean reaction time ($p = 0.19$) mean scores did not.

Conclusions: Vitamin D supplementation not only improves some behavioral problems but may prevent exacerbation in some symptoms of the disorder and reduce impulsivity.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) usually begins at 7 years of age and continues up to youth or adulthood [1]. The major symptoms of ADHD include a stable pattern of inattention, hyperactivity, impulsivity and distraction [1,2]. Secondary symptoms include aggression, social incompetence, peer conflict, and antisocial behavior [3]. This disorder is defined in three main groups: (1) mainly hyperactive, (2) mainly inattentive, and (3) combination of hyperactivity and inattention.

It seems that children with ADHD have more unusual energy without having the need for more sleep [4]. These children have difficulties in completing tasks [5]. Epidemiological studies report the rate of ADHD as 4–12% in general and 3–5% in Western countries in particular [1,5]. There is no firm evidence on the overall incidence and prevalence of ADHD in Iran but according to the provinces, the prevalence of ADHD in children of Isfahan city, the center of Iran is 4.6% [6]. There is no clear explanation for the causes of this disorder. Researchers believe that biogenetic factors such as the shortage, imbalance or inefficiency of dopamine, serotonin and noradrenaline play an important role in its occurrence [2,7]. Current studies mainly focus on genetic and environmental factors and the combination of both [8]. ADHD emerges along with some deficits in the prefrontal cortex of the brain [9].

Medications such as Ritalin, Dextroamphetamine and Strattera are the most common treatments. Despite considerable development in

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https://doi.org/10.1016/j.eujim.2018.10.006
Received 6 May 2018; Received in revised form 3 October 2018; Accepted 4 October 2018

psychiatric drugs, only 30–70% of afflicted adults respond to these medical interventions (the response rate in children is lower than this) [10]. The most effective treatment is controlling the disorder [11,12]. Researchers have found several cues to understanding this highly complicated phenomenon. They have discovered the role of nutrition [1,13,14] and micronutrients such as Omega3 [15,16], Zinc [16,17] and Magnesium [18] in controlling and improving its symptoms. Diet therapy is a simple and inexpensive method that is welcomed and accepted by parents [13].

Vitamin D plays known important and diverse roles in neuronal system including interfering with the signaling of calcium and the production of serotonin and glutathione [22,23].

Laboratory data shows that low levels of vitamin D are related to depression and schizophrenia in adults, but there is little evidence for the effects of this vitamin on the mental health of children. Vitamin D is a neuroactive steroid [18]. The receptor of vitamin D and related enzymes are found in the nerve cells of the substantia nigra, hippocampus, hypothalamus, and prefrontal cortex. Data show that the shortage of vitamin D during the growth period of the brain leads to destructive effects on the dopaminergic system. Vitamin D plays a role in the proliferation and differentiation of brain cells (axonal growth) and increase in antioxidant capacity and hence protection against oxidative stress and adjustment of neurotrophic factors (such as the brain growth factor) [20].

Based on a study conducted in 2015, researchers discovered the relationship between the 25(OH) Vitamin D serum level of the mother in pregnancy and reduction of quasi-ADHD symptoms in the infant [21].

There is evidence confirming the role of vitamin D in regulating the synthesis of serotonin through tryptophan hydroxylase 2 enzymes [22]. Apart from its mentioned roles, vitamin D plays a direct role in regulating the signaling of calcium and decreasing the adjustment of the Ca ion in the brain (a high concentration of Ca ions in the brain leads to toxicity while vitamin D can dilute such concentrations) [23].

Primary evidence has shown that increase in the concentration of 25(OH) vitamin D serum decreases ADHD symptoms and vice versa [24,25]. The main objective of this research was to determine the effects of vitamin D supplementary intake in 6–13 year-old students with ADHD in Isfahan.

2. Methodology

This study was designed as a double-blind, randomized, controlled clinical trial. From schools, 84 students with ages between 6 and 13 year were recruited. The study was conducted in Isfahan, central of Iran and approved by the ethic committee of Isfahan University of Medical Sciences (Ethical code: R.MUI.REC.1394.3.886).

Study participants consisted of students who had been referred to the Khorshid University Hospital Inpatient Psychiatric Unit and had been diagnosed as ADHD cases. A total of 84 students were included in the study. From these, in control group, 7 did not continue with the study due to poor compliance (5 subjects), and 2 subjects refused to take Vitamin D. In intervention group, 3 subjects due to poor compliance and 3 subjects abstained to continue participation due to personal reasons. Therefore, 71 subjects completed the study. For all students ADHD was diagnosed by a child and adolescent psychiatrist according to the DSMIV index. In this study, all participants took only Ritalin as a routine medicine with similar doses.

Exclusion criteria were BMI higher than 25, any apparent chronic disease, intake of Vitamin D supplement, Omega 3 or zinc during the past two months, use of non-pharmacological treatments such as neurofeedback, play therapy or any vision or movement disabilities and the subjects who unable to provide informed consent.

The patients received one daily vitamin D3 tablet (1000 IU) or placebo and taken after lunch for three months. Vitamin D tablets were obtained from Daana Pharmaceutical Company in Iran. Demographic characteristics, duration of exposure to direct sunlight using questionnaire, fasting serum vitamin D level and psychiatric status scores (SDQ and CPQ) were measured before and at the end of supplement administration period.

Participants signed informed consent after receiving explanation of the study protocols. Any parent's dissatisfaction during the project led to the omission of their children from this research.

2.1. Persian-language version of Psychiatric assessment tools

2.1.1. SDQ (Strengths and Difficulties Questionnaire)

This questionnaire includes 25 questions and was completed by parents (SDQP) and teachers (SDQT), with results being obtained numerically. The questionnaire has 5 scales each constituted by five questions, and included; emotional problems, behavioral problems, hyperactivity, problems with peers, and social behavior scales. The score of each scale ranges between 0 and 10, and each question is assigned a score between 0 and 2. This questionnaire has been validated in Iran and is considered valid and reliable [33,34].

2.1.2. CPQ (Connors Parent Questionnaire)

In order to achieve higher precision, the CPQ was used in addition to the SDQ. The Connors Parent Questionnaire has 26 questions and has been validated by the Iranian Institute of Cognitive Sciences [35]. The total score of the test ranges from 26 to 104. If the obtained score is higher than 34, it can be concluded that there exists a case of attention deficit disorder. The higher the score, the stronger the disorder.

2.1.3. CPT (Continuous Performance Test)

Attention was tested by CPT. The test is conducted by computer and its length of time is adjustable; in this research it was adjusted to take 5 min. In the test, 120 images were shown on the monitor; each image lasted for 8 s after which another image was substituted. 15 of the 120 images were repeated, and on seeing an image shown before, the respondents were to tab the space bar. This test determines the level of attention, impulsivity and mean reaction time of each respondent [36]. The Game Card and Joystick versions were used in this research.

3. Baecke questionnaire

The physical activity of the participants in both the intervention and control groups was assessed by the Baecke international questionnaire, and the obtained values were analyzed with SPSS software. The questionnaire contained three variables including work, sport and leisure time. The values for the variables of sport and leisure time were obtained separately.

3.1. Statistical analysis

We used the paired and the independent-samples student's *t*-test to assess inter- and intra-group comparisons respectively while the chi-square was used to assess nominal variables. Normal distribution was checked by Kolmogorov–Smirnov test. After the intervention, if the two groups showed a significant difference compared to the beginning of the intervention, we used the Covariance Analysis Test (ANCOVA) to assess intra-group comparisons. Confounding variables including Neurofeedback, Maturity, exposure to direct sunlight, Parenting Education and play therapy. We reported the results as the mean ± standard deviation. $p < 0.05$ is considered as statistically significant. To analyze the data SPSS 20 was used.

4. Results

Six participants in the intervention group were excluded from the study due to their lack of cooperation, and seven subjects of the control group were excluded due to their unwillingness to go through the

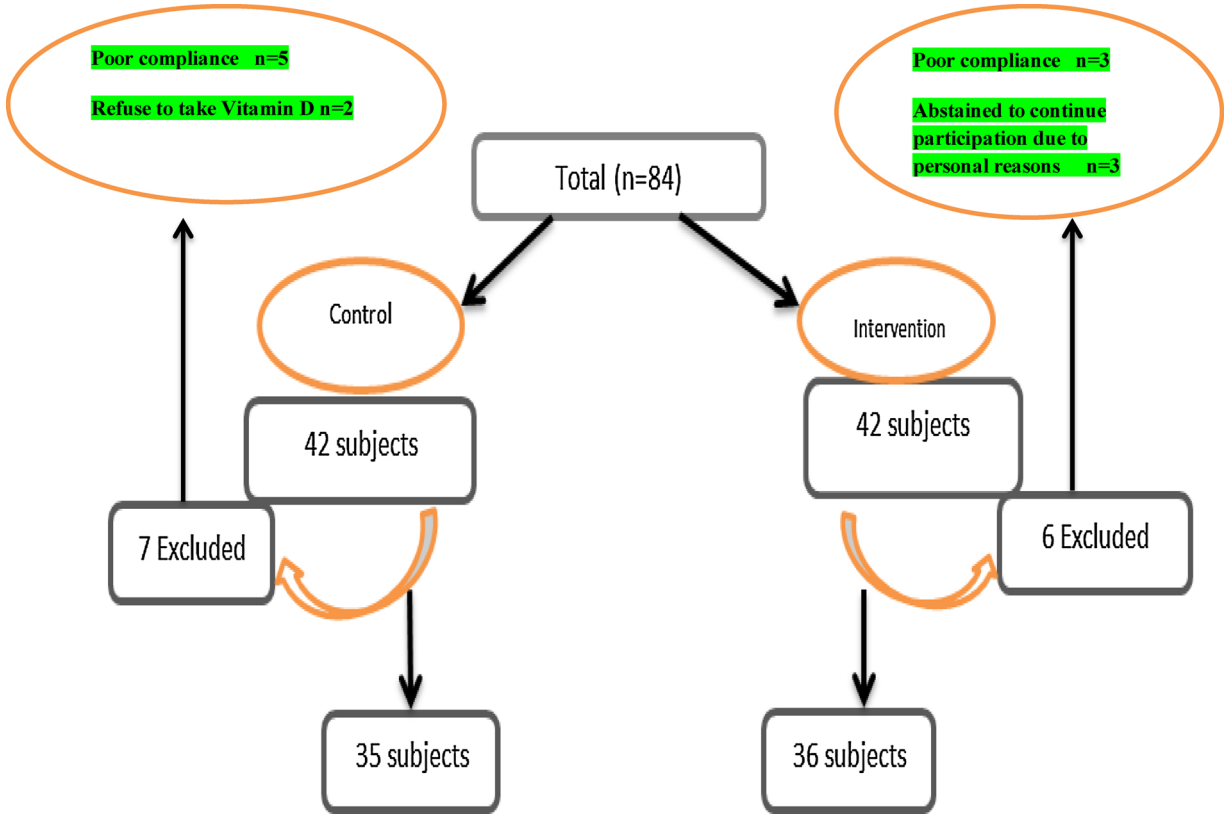

Fig. 1. Flowchart of study.

bleeding procedure needle phobia to go through the bleeding procedure for the second step of the research. Thus, considering these exclusions, at the end of the research, 71 subjects (59 male and 12 female) completed the study (Fig. 1).

Table 1 shows that participants in both groups were controlled in terms of age, gender and BMI. The mean scores of the leisure time and support sport variables showed no significant difference between the two groups using the Baecke Questionnaire ($p = 0.25$, $p = 0.89$ respectively). Moreover, as Table 1 shows, the mean amounts of vitamin D intake from food (Vit D-FR) made no significant difference for either group during the intervention ($p = 0.38$).

Table 2 shows that the mean scores of CPQ after the intervention was significantly lower in the intervention group compared to the control group ($p_1 = 0.002$). The difference between the mean scores of CPQ before and after intervention through the paired t-test in the control group was increasingly significant ($p = 0.001$) but in the intervention group, decreasingly significant ($p = 0.001$).

Moreover, Table 2 shows that the mean scores of SDQP in both groups was significantly different before the intervention ($p_1 = 0.001$).

Table 1
Descriptive characteristics of the subjects before and after the intervention.

Variable	Intervention ($n = 36$) Mean ± SD	Control ($n = 35$) Mean ± SD	p
Age (years)	9.20 ± 1.84	9.04 ± 1.2	0.68
Sex	83.3%(M), 16.7%(F)	82.9%(M), 17.1%(F)	0.60
BMI_1	16.53 ± 3.01	17.25 ± 3.22	0.34
BMI_2	17.11 ± 3.03	17.59 ± 3.49	0.53
Leisure time score	2.72 + 0.73	2.51 ± 0.44	0.89
Sport score	2.96 + 0.75	2.93 ± 0.79	0.25
25(OH)vitamin $D_{1(IU)}$	47.01 ± 17.05	59.63 ± 25.88	0.02
25(OH)vitamin $D_{2(IU)}$	84.37 ± 17.43	54.94 ± 20.07	0.001
Vit D-FR(μg)	0.63 ± 0.55	0.56 ± 0.45	0.38

Food record (FR). 1 = before intervention, 2 = after intervention.

Table 2
Mean scores of CPQ and SDQ variables.

Variable	Intervention ($n = 36$) Mean ± SD	Control ($n = 35$) Mean ± SD	P1	P2 (Ancova)
CPQ1	69.27 ± 12.33	68.91 ± 14.82	0.93	
CPQ2	65.97 ± 14.5	77.69 ± 16.66	0.002	
SDQP1	21.50 ± 4.81	17.23 ± 4.37	0.001	
SDQP2	18.08 ± 5.4	21.00 ± 4.97	0.02	0.001
SDQT1	17.72 ± 6.6	17.17 ± 6.1	0.71	
SDQT2	16.36 ± 6.7	25.80 ± 5.52	0.01	

1 = before intervention, 2 = after intervention. CPQ (Conners Parent Questionnaire), SDQP (Strengths and Difficulties Questionnaire Parent Version), SDQT (Strengths and Difficulties Questionnaire Teacher Version).

For this reason the ANCOVA test was used to determine the differences of SDQP in the two groups. Accordingly, the mean score of SDQP after the intervention was significantly lower in the intervention group as compared to the control group ($p_2 = 0.001$). Also, the difference of the mean scores in the SDQT scale was significant after the intervention ($p = 0.01$).

As Table 3 shows, in CPT, the difference of the mean scores of impulsivity in the two groups was not significant before, ($p = 0.62$) but was after the intervention ($p = 0.02$). The difference between the mean scores of attention before and after the intervention was not significant ($p = 0.42$ and $p = 0.11$ respectively). The difference between the mean scores of Mean Reaction Time before and after the intervention was not significant either ($p = 0.69$ and $p = 0.19$ respectively).

As Table 4 shows, the difference of the mean scores in the SDQP scale (emotion and peer difficulties) was significant in both groups before the intervention ($p = 0.02$, $p = 0.002$), and using the Ancova test, results showed a significant difference after the intervention as well ($p = 0.001$, $p = 0.03$). The difference in the mean scores of the behavioral difficulties scale was significant in both groups after the

Table 3
Mean scores area of CPT variables.

	Intervention (n = 36) Mean ± SD	Control (n = 35) Mean ± SD	P1
CPT1			
Attention	8.31 ± 4.41	9.14 ± 4.37	0.43
Impulsive	11.38 ± 2.24	13.22 ± 2.94	0.62
MRT[a]	0.96 ± .50	0.96 ± .50	0.69
CPT2			
Attention	11.28 ± 3.57	9.68 ± 4.67	0.11
Impulsive	4.92 ± 4.94	13.34 ± 3.64	0.02
MRT	0.96 ± .50	0.90 ± .10	0.19

1 = before intervention, 2 = after intervention.
[a] Mean Reaction Time, P1 = Independent t-test.

Table 4
Comparison of SDQP and SDQT questionnaires scales before and after intervention in the two groups.

Criterion of SDQP	Intervention (n = 36) Mean ± SD	Control (n = 35) Mean ± SD	P1	P2 (ANVOCA)
SDQP1				
Emotion D	4.66 ± 2.3	3.33 ± 2.6	0.02	
Relationship PD	4.53 ± 2.1	3.11 ± 1.6	0.002	
Social	6.86 ± 1.9	7.23 ± 2.2	0.46	
Behavioral D	4.05 ± 1.7	3.71 ± 2.1	0.45	
Hyperactivity	7.69 ± 1.8	6.97 ± 2.0	0.11	
SDQP2				
Emotion D	4.11 ± 1.9	4.6 ± 2.5	0.36	0.001
Relationship PD	3.94 ± 1.8	4.26 ± 1.6	0.45	0.03
Social	7.22 ± 1.8	7.06 ± 1.9	0.71	
Behavioral D	3.67 ± 1.9	4.68 ± 2.3	0.04	
Hyperactivity	6.47 ± 1.9	7.25 ± 1.9	0.08	
SDQT1				
Emotion D	4.36 ± 2.8	3.20 ± 1.9	0.05	
Relationship PD	4.05 ± 1.8	4.43 ± 1.7	0.39	
Social	5.44 ± 2.1	5.83 ± 2.3	0.47	
Behavioral D	3.33 ± 2.4	3.40 ± 2.5	0.91	
Hyperactivity	5.72 ± 2.4	6.40 ± 2.4	0.24	
SDQT2				
Emotion D	3.89 ± 2.2	4.89 ± 2.0	0.07	0.001
Relationship PD	4.08 ± 1.6	4.72 ± 2.2	0.15	
Social	6.47 ± 2.4	4.94 ± 2.6	0.01	
Behavioral D	2.92 ± 2.1	4.54 ± 2.4	0.004	
Hyperactivity	5.17 ± 2.6	7.06 ± 2.3	0.002	

1 = before intervention, 2 = after intervention, D = Difficulties, PD = Peers difficulties.

intervention ($p = 0.04$). The difference of the mean scores of the SDQP1 and SDQP2 questionnaires determined by the paired t-test in the control group showed increasing significance ($p < 0.001$) but in the intervention group decreasing significance before and after the intervention ($p < 0.001$).

Moreover, Table 4 shows that the difference of the mean scores in the SDQT scale (emotional and behavioral difficulties) was significant after the intervention ($p = 0.001$, $p = 0.04$). The difference of the mean scores of the hyperactivity scale was significant after the intervention ($p = 0.002$). The difference of the mean scores of the social behavioral scale was not significant in the groups before the intervention ($p = 0.47$), but was after the intervention such that in the intervention group it increased positively in contrast to the other scales ($p = 0.01$). The inter-group mean score of the SDQT questionnaire in both control and intervention group was not significant in the paired t-test ($p = 0.12$ and $p = 0.13$ respectively).

5. Discussion

In this research, the two groups were similar to each other in terms of participant age, gender, BMI, physical activity level, sun exposure, type and dose of medication. Vitamin D supplementation significantly increased the serum level of this vitamin in interventional group compared with controls. This intervention also was concurrent with a significant decrease in the mean scores of CPQ, SDQP, SDQT and impulsivity (using CPT) in intervention group, while the mean scores of the attention and mean reaction times (MRT) remained similar in the two groups.

Since there are very few studies in the literature on interventions based on the effect of vitamin D on ADHD, and since there are some similarities between ADHD and certain other disorders such as autism due to the performance of neurotransmitters, some studies relating to the effect of vitamin D on similar disorders will be discussed in this section.

In a similar study among children, Elshorbagy, et al assessed the effect of 25(OH) Vitamin D on ADHD. The results indicated that vitamin D cause improvement in cognitive function in the conceptual level, inattention, opposition, hyperactivity, and impulsivity domains but in the present study Vitamin D, improved impulsivity but not inattention. Recently, Mohammadpour et al. conducted a study to examine the effect of vitamin D supplementation as adjunctive therapy to treatment with methylphenidate on ADHD symptoms in children aged 5–12 years. They reported that ADHD symptoms decreased significantly in interventional group and there were no differences in symptoms assessed by the CPRS (Conner's Parent Rating Scale-Revised) and ADHD-RS (ADHD rating scale-IV) scales. Although Mohhamadpour's results were coextensive with those of our study, in the former; supplementation duration was 8 weeks with a dose of 2000 IU while in the latter the dose and duration were 1000 IU and 12 weeks respectively. Also, in Mohhamadpour's study the Conner's scale was used at three times (before, during and end of intervention) as well as before taking Ritalin in the morning and after taking it in the afternoon. Focus on more instruments; sample size and duration are the advantage of our study [26].

In recent decades, researchers have studied the effects of vitamin D on some disorders such as autism, schizophrenia, depression, anxiety, Parkinson and mood disorders. The results of such studies are contradictory. In one such study, researchers compared the outcome of vitamin D deficit in normal individuals and those with Parkinson disease. The results showed that the 25(OH)vitamin D serum level in the latter group was lower [27].

Another interventional study aimed at investigating the effect of vitamin D supplementation on the cognitive and emotional performance of young adults during a 6-week period with a daily dosage of 5000 IU on two (intervention and control) groups. This study reported no positive results. In this study, the researchers focused on short-term memory and prevention of emotional expression [26]. The important points of this study are the short period of supplementation and the normality of the participants. These points would have been effective on the lack of positive results in the research.

Another study investigated the relationship between vitamin D deficit and depression, seasonal disorder and schizophrenia during a 16-month period on 104 teenagers. Subjects with a lower level of vitamin D suffered from the mentioned disorders more than other subjects [28]. In yet another study, researchers focused on the relationship between 25(OH) vitamin D serum level and autism. The level of vitamin D in individuals with Autism Spectrum Disorder (ASD) was reported to be lower in comparison with normal individuals [29]. Like ADHD, in these disorders the synthesis and performance of the neurotransmitters was abnormal.

In a case control study, Bener et al. conducted a research to find the relationship between a low level of vitamin D and ADHD. In this study, the researchers studied the 25(OH) vitamin D serum level in 60

diseased and 30 normal individuals. Specifically, they reported that the 25(OH) vitamin D serum level in the diseased cases was lower than that of the normal individuals. Their results were significant ($p = 0.001$) [31]. The researchers proposed that polymorphism in the genes of proteins which attach themselves to this vitamin is a main cause of vitamin D deficit. The confirmation of this theory requires genetic studies on cases of this disorder [32].

In a similar epidemiological study on 5–18 year-olds, Kamal et al. studied and measured the 25(OH) vitamin D serum level in two (diseased and normal) groups. Their results showed a significant relationship ($p < 0.0001$) between ADHD and vitamin D [33].

In the past two years, the serum level of vitamin D has been measured in children with ADHD in four different studies. Research was conducted in Isfahan, Iran. In all of these studies, the serum level of this vitamin in ADHD cases was significantly lower than that in normal subjects, and hence they suggest a probable relationship between vitamin D deficit and ADHD [3,34–36]. The results of this research (whose sample sizes are different) show positive and convergent results. These studies have reinforced the relationship between vitamin D deficit and ADHD, though the cause of such a relationship is still vague and unclear. This can be due to genetic differences in the genes that encode the enzymes of the metabolism paths of this vitamin and polymorphism in the VDR (Vitamin D Receptor) gene; however, more research is required to find such a relationship.

Since, the response to drug therapy in children affected by ADHD is less than 30% and drugs have different side effects, the results of the present study suggest promising new therapeutic for this disorder.

The psychological status were also evaluated just after the termination of vitamin supplementation, therefore the real influence, Durability, and possible disadvantages of this treatment in more prolonged terms remains obscure.

The results of this study support the idea that vitamin D supplementation may improve the symptoms of ADHD in children. The observed improvements were especially prominent in emotional and behavioral difficulties. The serum concentrations of the Vitamin D in the subjects at the beginning of this study were within the recommended values, and therefore, the observed effects cannot be simply attributed to correction of vitamin D deficiency.

5.1. Limitations

Supplementation with only a single dose and within a single period (three months) are two of the major limitations of this study. Also, assessment of the all type of ADHD (inattention, hyperactivity, impulsivity and distraction) in this study instead of one type is another limitation.

6. Conclusion

The findings of the present study show that vitamin D supplementation is apparently effective in improving impulsivity and some conduct disorders. The effectiveness of this supplementation may be more pronounced if we increased the dosage of the supplement and increased the sample size. Undoubtedly, it is necessary to conduct more research in this area. Moreover, it seems necessary to conduct intervention studies in order to improve the symptoms of ADHD with minimum side effects.

Acknowledgments

Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran supported present study.

The authors declare no conflict of interest.

Conflict of interest

The authors declare no conflict of interest.

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