Original Article

The Impact of Vitamin D Supplementation on Attention-Deficit Hyperactivity Disorder in Children

Annals of Pharmacotherapy
1–9

DOI: 10.1177/1060028018759471
journals.sagepub.com/home/aop
SAGE

Hatem Hamed Elshorbagy, MD[1], Naglaa Fathy Barseem, MD[1], Waleed Elsayed Abdelghani, MD[2], Hany Abdelaziz Ibrahim Suliman, MD[2], Ashraf Hamed Al-shokary, MD[2], Sameh Elsayed Abdulsamea, MD[2], Akram Elshafey Elsadek, MD[2], Yehia Hamed Abdel Maksoud, MD[2], and Dalia Mohamed Abd El-Hassib Nour El Din, MD[2]

Abstract

Background: The role of nutrients and dietary factors in attention-deficit hyperactivity disorder (ADHD) remains unclear. **Objectives:** The primary objective was to evaluate the serum vitamin D level in children with a diagnosis of ADHD. The secondary objective was to detect the effect of vitamin D supplementation on cognitive function in those with vitamin D deficiency. **Methods:** A total of 50 children with ADHD and 40 healthy controls were included in the study. We measured the serum level of vitamin D. Patients with vitamin D deficiency were subdivided into 2 groups: one with vitamin D supplementation and the other without vitamin D supplementation. Further assessment and follow-up of children with ADHD was done. The Wisconsin Card Sorting Test, Conners' Parent Rating Scale, and Wechsler Intelligence Scale for Children were performed at baseline and follow-up in all cohorts with an ADHD diagnosis. **Results:** The diagnosis of vitamin D deficiency was significantly greater in children with ADHD compared with the control group ($P < 0.05$). Children with ADHD had significantly ($P = 0.0009$) lower values of serum vitamin D (17.23 ± 8.98) than the control group(31.47 ± 14.42). The group receiving vitamin D supplementation demonstrated improvement in cognitive function in the conceptual level, inattention, opposition, hyperactivity, and impulsivity domains. **Conclusion:** Vitamin D supplementation in children with ADHD may improve cognitive function.

Keywords
vitamin D, supplementation, children, ADHD

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder, characterized by inattention, hyperactivity, and/or impulsivity, that affects 2% to 9% of all children and adolescents.[1] ADHD can affect the function and development of children with this disorder, and other family members, peers, and teachers can also be affected by this disorder. It is one of the leading causes of disruptive behaviors and academic underachievement in school.[2] Drug therapy is the mainstay of treatment—namely, amphetamines and methylphenidates—but there are limitations to drug interventions. Many parents prefer not to start drug therapy for fear of adverse effects and may seek alternative treatments. Up to 30% of patients with ADHD are refractive to treatment with stimulant medication.[3]

A National Health Interview Study demonstrated that 8.9% of studied children had been diagnosed with ADHD, and of those, 24.7% used at least 1 type of complementary and alternative medical therapy.[4] Although the link between nutrient deficiencies and ADHD is still a matter of debate, the role of nutrition in the prevention and treatment of clinical manifestations of the disease has been a topic of recent interest.[5] It has been postulated that vitamin D is important to the development of the brain, especially during the prenatal and early neonatal period.[5,6] It was concluded that vitamin D is essential for brain development through different mechanisms, and lack of vitamin D during early fetal life and childhood affects brain structure and function.[7-9] However, some studies reported that mother's vitamin D

[1]Menofia University, Shebeeen Elkom, Egypt
[2]Benha University, Egypt

Corresponding Author:
Hatem H. Elshorbagy, Department of Pediatrics, Menofia University, Shebeeen Elkom, 1111, Egypt.
Email: shorbagy732000@yahoo.com

Table 1. Baseline Demographic Data.

Participants	Sex		Age (years), Mean ± SD	Vitamin D Level (ng/mL), Mean ± SD
	Male, n (%)	Female, n (%)		
ADHD, n = 50	28 (56)	22 (44)	9.31 ± 2.60	17.23 ± 8.98
Control, n = 40	21 (52.5)	19 (47.5)	8.80 ± 3.72	31.47 ± 14.42
P value	0.1[a]		0.4[b]	0.0009[b]

Abbreviation: ADHD, attention-deficit hyperactivity disorder.
[a]χ^2 Test.
[b]Student *t*-test.

during pregnancy had no association with behavioral problems in the offspring, including symptoms of ADHD.[10,11] However, limited studies have been conducted to clarify the role of vitamin D in ADHD. Vitamin D had been shown to be important to brain development in animal and human studies.[12] 25-Hydroxyvitamin D [25 (OH)D] is the best measure of vitamin D and reflects different sources of vitamin D like cutaneous synthesis, food intake, and supplementation. 1,25-dihydroxyvitamin D is the active form of vitamin D but not considered a useful measure of vitamin D status in the body because of its short half-life and persistence of normal levels even in the deficiency states secondary to upregulation of the 1α-hydroxylase enzyme[13] Vitamin D receptors and 1α-hydroxylase enzyme, an enzyme responsible for the formation of the active form of vitamin D, are widely distributed in the central nervous system, mainly in the neuronal cells of the substantia nigra, hippocampus, hypothalamus, prefrontal cortex, and cingulated gyrus. Indeed, many of these regions have been implicated in the pathogenesis of ADHD.[14]

Sun exposure plays a role in vitamin D synthesis in the skin. Despite sunlight, the prevalence of vitamin D deficiency is high in Persian Gulf countries. It was found that 70% of young girls in Iran and 80% in Saudi Arabia suffered from vitamin D deficiency.[15] Although sunlight plays a role in the homeostasis of vitamin D in the blood, exposure to sunlight alone is not enough to cure vitamin D deficiency.[16]

There are several mechanisms for decreasing symptoms of ADHD through vitamin D supplementation. Vitamin D is essential for the production of dopamine and norepinephrine, neurotransmitters responsible for reducing the negative symptoms of ADHD. In addition, it increases the production of acetylcholine, which helps in maintaining focus and concentration and encourages the growth of nerve cells for executive functions.[17,18]

The aim of this study was to assess vitamin D levels in children with ADHD in comparison with vitamin D levels in children without an ADHD diagnosis. A secondary aim was to detect the effect of vitamin D supplementation as an adjunctive therapy to improve cognitive function in vitamin D–deficient patients.

Patients and Methods

This case-control prospective interventional study was conducted in 50 children with ADHD and 40 healthy controls. The study was conducted from December 2015 to January 2017 after informed consent. Children with ADHD were enrolled from the pediatric neuropsychiatric outpatient clinic, Al Hada and Taif military hospitals, Saudi Arabia. There were 28 male and 22 female participants (Table 1), with ages ranging from 7 to 14 years (mean 9.3 ± 2.6 years).

A control group included 40 healthy children matched for age, sex, nutritional status, and body mass index, with no history of vitamin D supplementation. Controls were chosen among non-ADHD children selected from those who visited the primary health care centers for any reason other than acute or chronic disease. There were 21 boys and 19 girls. Their ages ranged from 6 to 13 years, with a mean of 8.8 ± (3.7) years (Table 1). An independent research board had reviewed and approved the study protocol before the study was conducted. All ethical guidelines on the 1964 Declaration of Helsinki and its later amendments were taken into account.

Exclusion criteria were the following: liver disease with impaired liver function tests; kidney disease with a rise of at least 50% in serum creatinine or impaired creatinine clearance; thyroid and parathyroid disorders; fat malabsorption; history of head injuries, seizures, autism, or mental retardation with IQ less than 70; and use of vitamin D or vitamin D–containing products 3 months prior to the study and drugs interfering with vitamin D metabolism, such as phenobarbital, phenytoin, antituberculosis drugs, cholesterol-lowering statin drugs, and thiazide diuretics. Patients with an HIV diagnosis as both the disease state itself as well as HAART (highly active antiretroviral therapy) can interfere with vitamin D metabolism.

ADHD was diagnosed by a child and adolescent psychiatrist using the *Statistical Manual of Mental Disorders* diagnostic criteria (DSM-IV) through a face-to-face interview for the child and his parents.[19] All children with ADHD received methylphenidate 0.3 to 1 mg/kg/d 3 times a day (began with 0.3 mg/kg and titrated gradually to the optimum dose, 1 mg/kg).

Each patient was subjected to the following: a detailed medical history, including perinatal history; developmental history; and family history of similar cases. Data were collected in regard to mean duration of ADHD diagnosis, number of previous stimulant or nonstimulant trials, current ADHD therapy, or other current psychiatric diagnoses as well as dietary intake, physical activity, and sun exposure. Clinical examination included the following: anthropometry, physical examination, and neurological examination.

Dietary intake of participants, physical activity, and sun exposure were assessed as possible confounders at baseline and at the end point of intervention. Food diaries were measured by recall questionnaires of 3 nonconsecutive 24-hour periods. Information was obtained about food intake, including energy, macronutrients, and micronutrients. Evaluation of physical activity was assessed through use of an international physical activity questionnaire.

Assessment of sun exposure was done by collecting data about the duration and part of the body that was exposed to the sun and use of sunscreen cream. Significant sun exposure over the course of the trial period was defined by self-report of spending more than 30 minutes outside without sunscreen with arms and legs or more exposed.

Determination of Vitamin D Status

A venous blood sample of 3 mL was taken from each participant in the study and the serum separated and stored at −70°C until the time of analysis. Serum [25 (OH)D] was measured using a commercially available kit (DiaSorin Corporate Headquarter, Saluggia, Italy). Serum [25 (OH)D] was measured again after complete supplementation using the competitive binding radioimmunoassay technique.[20] The values of serum vitamin D level were classified into 4 categories according to analysis of the serum:(1) normal (30-100 ng/mL); (2) low (10-29 ng/mL); (3) severely low (<10 ng/mL); (4) toxic (>100 ng/mL).[21]

The 2 groups in the ADHD cohort were also assessed through the use of the following psychiatric scales:

An Arabic version of Conners' Parent Rating Scale was used for detection of the severity of ADHD.[22] We scored items related to hyperactivity, inattention, oppositional, and impulsivity. Conners' Parent Rating Scale is a 27-item scale that is usually scored by patents. Ratings on the questionnaire ranged from 0 (*never or rarely*) to 3 (*very often*). A total score is derived from the scale, and the cutoff score of 15 has been established. Raw scores were converted to *T*-scores based on gender and age.[23]

Wisconsin's Card Sorting Test (WCST) is a neuropsychological test to measure the executive function. A computerized version of the task was used (Microsoft Windows-compatible version 4.0), which automatically scores the test in contrast to the manual version.[16] This requires the examinee to discern the sort criterion of a set of cards based on "correct" versus "incorrect" feedback given by the examiner. After correctly matching a card according to a stimulus for 10 consecutive trials, the matching feature changes. This occurs 6 times or until all 128 cards are administered. Successful performance on the WCST requires that an individual determine the correct response in dimension and then maintain responding to that dimension.[24]

An Arabic version of the Wechsler Intelligence Scale for children (WISC) for assessment of intelligence quotient (IQ).[16] The test was used according to the standard procedure. The WISC consists of 11 subtests: 6 subtests of verbal intelligence (information, comprehension, arithmetic, similarities, digit span, and vocabulary) and 5 subtests of nonverbal, performance intelligence (coding, picture completion, block design, picture arrangement, and object assembly). Scores derived from these subtests include the full-scale IQ, verbal IQ, and performance IQ.[25]

According to the results of vitamin D assays, children with ADHD were divided into 2 groups: group 1(40 patients) included children with ADHD with vitamin D deficiency, and group 2(10 patients) included children with ADHD with normal vitamin D levels. Children with ADHD who showed a deficiency in vitamin D were stratified by gender and randomly assigned in a double-blind fashion in a 1:1 ratio to the vitamin D supplementation group or the placebo group by permuted-block randomization. Group 1A included 20 children with ADHD and vitamin D deficiency who received supplementation with vitamin D as an adjuvant therapy to the standard treatment. Group 1B included 20 children with ADHD and vitamin D deficiency who received the standard treatment and placebo without supplementation with vitamin D.

All children with ADHD received methylphenidate in a proper dose after gradual titration; 72% of the intervention group was previously on methylphenidate compared with 78% in the placebo group. Based on randomization, vitamin D or placebo had to be taken every day for 12 weeks by patients added to methylphenidate. Vitamin D and placebo were identical in appearance to guarantee blinding.

Vitamin D supplementation was done in the form of cholecalciferol in a dose of 3000 IU daily for 12 weeks in addition to methylphenidate.[21] Serum [25 (OH)D] was measured again after complete supplementation, and the 2 groups were compared using Conner's' Parent Rating Scale and WCST. Adherence to the vitamin D or methylphenidate was assessed by counting the remaining pills and measuring serum 25(OH)D. Patients were considered compliant if they consumed more than 80% of supplements.

Outcome Measures

The primary outcome measure was changes in the clinical symptoms as evaluated by Conner's Parent Rating Scale, which was completed by parents and used to measure ADHD symptom severity in the last 4 weeks. Secondary outcomes were ADHD domains and Weekly Parent Ratings of Behavior. ADHD domains completed by a trained interviewer include changes in categories completion, conceptual level, impulsivity, inattention, hyperactivity, and oppositional domains. The safety of treatment was checked using a side effects questionnaire.

Statistical Analysis

Data and variables were analyzed using SPSS version 16.0 (Chicago, IL). Quantitative data are presented as means ± SD. The χ^2 test was used to compare categorical data. All variables were assessed for normality by Kolmogorov-Smirnov test. The Student *t*-test was used to test differences in means, and the Mann-Whitney *U* test was used for nonparametric statistics. The paired *t*-test and Wilcoxon test were used to investigate within-group differences. Confounding factors were adjusted using the analysis of covariance. For the assessment of symptoms severity in ADHD, the *T*-score was used for Conners' Parent Rating Scale questionnaires that were obtained by transformation based on normative data adjusted for age and gender. The *P* value was considered significant when below 0.05. Correlation analysis was done using Spearman's rank correlation.

Results

This study was conducted in 90 children, 50 of whom were in the ADHD cohort and 40 in the control group. A total of 77 patients were screened for study inclusion, and 27 did not meet entry criteria. Out of the 40 patients, 35 completed the study. The study had a small difference that was not significant in terms of the attrition rates between the 2 arms: 4 (20%) in the intervention group and 1 (5%) in the placebo group; $P = 0.06$ (Figure 1). Adherence was 100% in the remaining participants.

Regarding the age and gender, there was no statistically significant difference between patient and control groups in their vitamin D levels. The mean durations of ADHD diagnosis were 13.2 ± 3.6 and 14.3 ± 2.8 months in the vitamin D supplemented group (group 1A) and placebo group (group 1B), respectively. There were 6 incomplete trials, usually because of side effects (4 for methylphenidate and 2 for amphetamine) in the vitamin D supplemented group (group 1A) compared with 4 trials (3 for methylphenidate and 1 for amphetamine) in the placebo group (group 1B). All patients received standard management (methylphenidate and behavioral therapy).

Comorbid psychiatric disorders were reported in 9 (45%) patients in group 1A compared with 8 (40%) patients in group 1B. Specific developmental disorder of scholastic skills was the most prevalent comorbidity in this study (45%) followed by Oppositional Defiant Disorder (28%). No statistically significant differences were reported in regard to the mean duration of ADHD diagnosis, number of previous stimulant or nonstimulant trials, current ADHD therapy, or other current psychiatric diagnoses in both groups.

However, statistically significantly ($P < 0.001$) lower values of serum vitamin D levels were reported in children with ADHD compared with controls (Table 1). The ADHD group showed subnormal levels of vitamin D in 80% (group 1), whereas the remaining 20% had normal serum vitamin D levels (group 2). The control group showed subnormal and normal levels in 30% and 52.5%, respectively. However, none of both groups showed toxic levels of vitamin D. Statistical analysis showed a significant difference (*P* value < 0.05) in the serum vitamin D levels between the ADHD and control groups (Table 2).

At baseline, both groups of patients with ADHD (group 1, group 2) showed no statistically significant differences in the demographic data. Moreover, no differences were reported in the energy and nutrient intake based on 3-day food diaries analysis, physical activity, and assessment of sun exposure before and after the end of the therapeutic trials between the 2 groups.

Also, both groups of patients with ADHD (group 1, group 2) showed no statistically significant differences regarding different psychiatric scales at the beginning of the study (Table 3). According to the baseline vitamin D levels and psychiatric scale measurements, the correlation of serum vitamin D level to psychiatric scales revealed a positive correlation between serum vitamin D level and the total IQ scores and a negative correlation between serum vitamin D level and the hyperactivity components of the Conner's Parent Rating Scale (Table 4).

After 12 weeks of vitamin D supplementation, there was a significant increase in serum levels of 25(OH)D (mean increase = 20.14 ng/mL; $P < 0.01$) in the vitamin D supplemented group (group 1A), and 82.6% of this group had 25(OH)D ≥30 ng/mL. However, the placebo group (group 1B) showed no significant changes (mean increase = 4.17 ng/mL, $P > 0.05$) in 25(OH)D levels.

Among children with ADHD who received vitamin D supplementation (group 1A), authors compared different psychiatric scales at baseline and at follow-up. A significant improvement was noted in conceptual level, inattention, and opposition as well as in hyperactivity and impulsivity (Table 5). However, children with ADHD without vitamin D supplementation (group 1B) did not show such improvement except in the oppositional domain (Table 5).

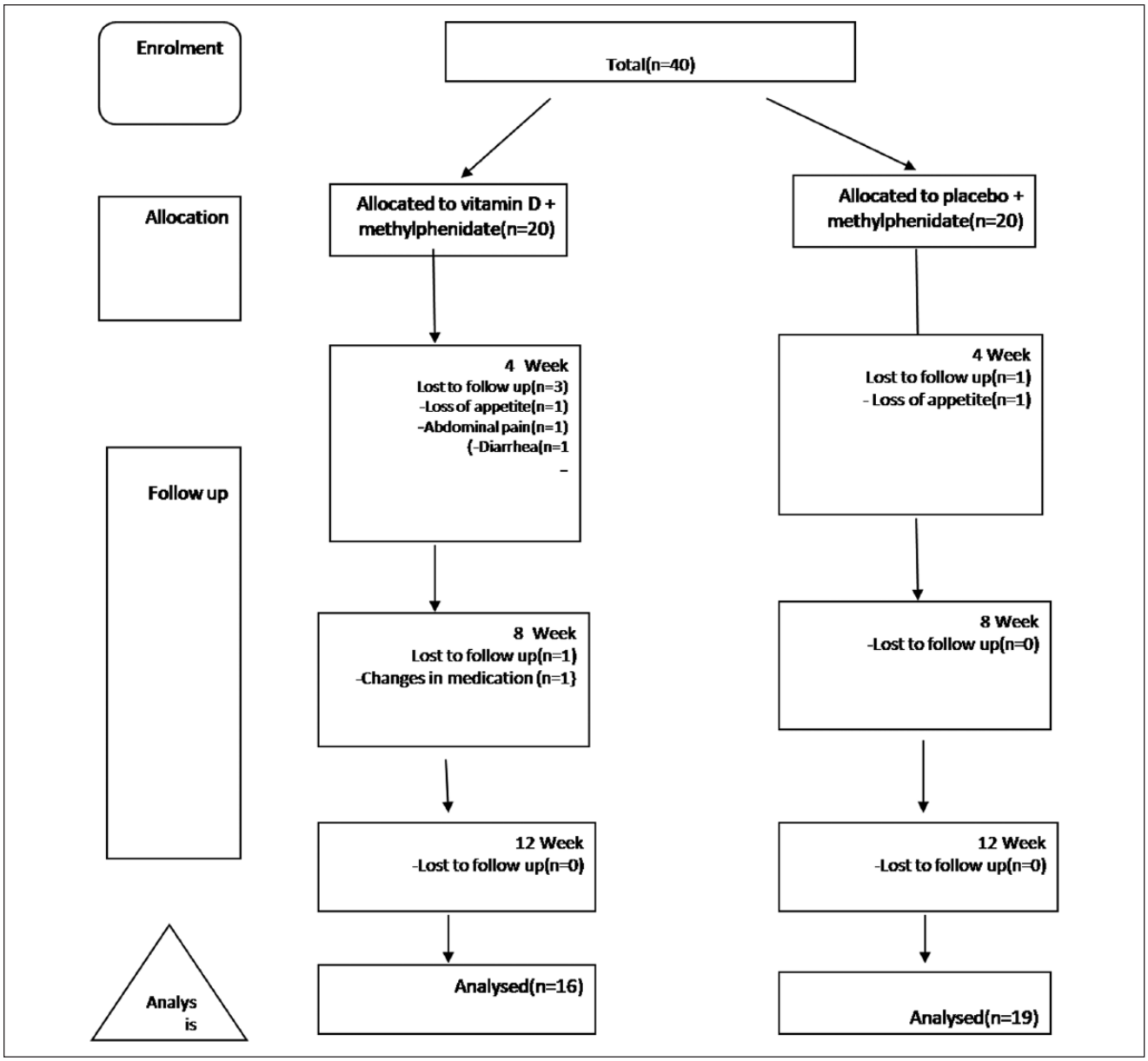

Figure 1. Flowchart of the attention-deficit hyperactivity disorder cohort.

Table 2. Comparison of Serum Vitamin D Levels of ADHD and Control Groups.

	Serum Vitamin D Levels (ng/mL)		
Variable	Very Low (<10 ng/mL), n (%)	Low (10-30 ng/mL), n (%)	Normal (30-100 ng/mL), n (%)
ADHD, n = 50	17 (34)	23 (46)	10 (20)
Control, n = 40	7 (17.5)	12 (30)	21 (52.5)
P value[a]	0.04	0.03	0.02

Abbreviation: ADHD, attention-deficit hyperactivity disorder.
[a]χ^2 Test.

At follow-up, the percentage of change in categories completion, conceptual level, impulsivity, and oppositional domains showed much improvement in group 1A rather than group 1B, but these findings were not statistically significant.

Table 3. Baseline Psychiatric Rating Scales in Children With ADHD With Vitamin D Deficiency (Group 1) and With Normal Vitamin D (Group 2).

Psychiatric Scales	Domains	ADHD With Vitamin D Deficiency (Group 1), Mean ± SD	ADHD With Normal Vitamin D (Group 2), Mean ± SD	*P* Value
Wechsler Scale				
Verbal skills	Comprehension	9.7 ± 2.2	9.3 ± 1.3	0.823
	Digit span	6.9 ± 2.8	6.1 ± 1.8	0.174
	Arithmetic	8.3 ± 3.1	7.4 ± 2.3	0.356
	Similarities	10.1 ± 3.0	10.7 ± 2.5	0.385
Performance skills	Picture completion	8.8 ± 2.3	8.9 ± 2.5	0.843
	Digit symbol	8.9 ± 3	8.2 ± 3.2	0.654
	Block design	8.5 ± 2.4	8.3 ± 2.2	0.631
Total IQ	Verbal IQ	98.9 ± 16.8	96.2 ± 7.8	0.621
	Performance IQ	96.7 ± 14.6	94.6 ± 13.4	0.873
	Total IQ	97.8 ± 15.7	95.4 ± 10.6	0.684
Wisconsin's Card Sorting Test	Categories completion	3.1 ± 2	3.2 ± 2.1	0.564
	Conceptual level	40.2 ± 26.4	45.4 ± 32.8	0.623
Conners' Parent Rating Scale	Inattention	70.8 ± 12.2	74.1 ± 9.4	0.473
	Hyperactivity	78.3 ± 8.8	77.5 ± 9.8	0.651
	Impulsivity	79.3 ± 9.2	81.3 ± 10.8	0.715
	Oppositional	66.4 ± 11.2	65.8 ± 10.4	0.491

Abbreviations: ADHD, attention-deficit hyperactivity disorder; IQ, intelligence quotient.

Table 4. Correlation Between Serum Levels of Vitamin D and Psychiatric Scales in Children With ADHD.[a]

Psychiatric Scales	Domains	*R*	*P*
Wechsler Scale	Total IQ	0.783	0.006
Wisconsin's Card Sorting Test	Categories completion	0.638	0.133
	Conceptual level	0.573	0.174
Conners' Parent Rating Scale	Inattention	−0.348	0.175
	Hyperactivity	−0.711	0.04
	Impulsivity	−0.953	0.617
	Oppositional	−0.994	0.431

Abbreviations: ADHD, attention-deficit hyperactivity disorder; IQ, intelligence quotient.
a *R: R* correlation coefficient; *P*, Spearman's rank correlation test; $P < 0.05$ is significant.

However, the percentage of change in the inattention and hyperactivity domains were statistically significant. Minor adverse effects of vitamin D supplementation were reported in 15% of patients (group 1A) in the form of mild abdominal pain, diarrhea, and loss of appetite. However, 5% of patients without vitamin D supplementation (group 1B) reported loss of appetite.

Discussion

Recently, the relationship between vitamin D and ADHD in children has been the focus of interest of many investigators. To our knowledge, this is the first therapeutic trial that examined the impact of vitamin D supplementation at a dose of 3000 IU daily for 8 weeks on cognitive function in children with ADHD.

In the past few years, an association has been found between vitamin D and many neuropsychiatric disorders.[26] In this study, we aimed to evaluate serum vitamin D levels in children with ADHD and the role of vitamin D supplementation in those with vitamin D deficiency.[27] The authors found that the ADHD group had a significantly higher percentage of vitamin D deficiency compared with the control group. Also, children with ADHD had significantly lower vitamin D levels than the control group. Our data were consistent with those reported from a study in Qatar where vitamin D levels were determined in 1331 children with ADHD (ages 5-18 years) and a similar number of healthy matched control children. Children with ADHD had significantly lower levels than the healthy controls.[27] Similar findings were reported by other studies, including a Turkish study which compared 60 children with ADHD, 7 to 18

Table 5. Comparison Between Psychiatric Scales at Baseline and at Follow-up in Children With ADHD With and Without Vitamin D Supplementation.[a]

		ADHD With Vitamin D Supplementation (Group 1A)		ADHD Without Vitamin D Supplementation (Group 1B)	
Variable	Timing	Mean ± SD	*P* Value	Mean ± SD	*P* Value
Categories completion	Before supplementation	3.50 ± 2.023	0.085	2.50 ± 2.061	0.643
	After supplementation	4.80 ± 0.56		3.30 ± 1.664	
Conceptual level	Before supplementation	48.60 ± 25.154	0.024	31.40 ± 21.562	0.0862
	After supplementation	83.20 ± 11.145		42.20 ± 20.694	
Inattention	Before supplementation	66.26 ± 14.628	0.037	74.20 ± 10.245	0.631
	After supplementation	55.48 ± 12.462		71.67 ± 9.654	
Hyperactivity	Before supplementation	80.38 ± 10.268	0.001	78.64 ± 9.543	0.964
	After supplementation	57.34 ± 11.342		75.92 ± 8.851	
Impulsivity	Before supplementation	78.50 ± 9.012	0.001	77.87 ± 10.439	0.0645
	After supplementation	57.36 ± 10.491		70.27 ± 9.564	
Oppositional	Before supplementation	63.486 ± 12.842	0.025	72.35 ± 10.052	0.034
	After supplementation	51.573 ± 10.045		66.64 ± 9.162	

Abbreviation: ADHD, attention-deficit hyperactivity disorder.
[a]SD, paired *t* test.

years old, with 30 age-matched control children. Other studies have reported similar findings.[28-30] However, Tolppanen et al[31] found no association between low levels of vitamin D and ADHD in his large study. Strøm et al[32] conducted a long-term follow-up study of children up to 22 years after birth and did not find an association between low D vitamin levels in the serum of the mothers during pregnancy and ADHD in their children. In a recent study conducted by Gustafsson et al,[33] vitamin D levels were analyzed in the serum collected from the child at the time of birth, which should reflect the prenatal status of vitamin D of the child. They then compared children who later developed ADHD with controls and reported findings similar to those of Strøm et al,[32] Gale et al,[10] and Whitehouse et al.[11] These studies were discordant with our results, unlike other studies in Qatar, Turkey, and Iran, which supported our findings.[27-29]

Although a high percentage of children with ADHD in our study had vitamin D deficiency, children in the control group were also found to have vitamin D deficiency. Therefore, vitamin D deficiency can be viewed as a world health problem. In our study, there was no significant difference among children with normal vitamin D (group 1) and children with a low level of vitamin D (group 2) in regard to the psychiatric scales at baseline. Additionally, not all patients with vitamin D supplementation improved at follow-up. This could be a result of the fact that ADHD is a multifactorial disorder resulting from an interplay of genetics and environmental factors.[34] The small sample size in our study is another limiting factor. We found a positive correlation between serum vitamin D and total IQ score and a negative correlation between serum vitamin D and hyperactivity score. Previous studies demonstrated that vitamin D and other micronutrient deficiencies were associated with poorer cognitive function and underachievement in children and adolescents.[17,35,36]

During follow-up of the supplemented group (group 1A) by psychiatric scales analysis, the authors found improvement in Conners' parents rating scores subitems, with significant improvements in conceptual level ($P = 0.024$), inattention ($P = 0.037$), hyperactivity ($P = 0.001$), impulsivity ($P = 0.001$), and oppositional domains ($P = 0.025$). However, follow-up of the nonsupplemented group (group 1B) showed that the cognitive function and Conners' scale subitems did not improve, except for the oppositional scale, because they were subjected to behavioral therapy. Vitamin D decreases symptoms in ADHD through modulation of neurotransmitters such as dopamine, norepinephrine, and acetylcholine.[17,18] The authors demonstrated that vitamin D supplementation for 12 weeks in conjunction with methylphenidate decreased symptoms of ADHD, notably inattention and hyperactivity.

In adult patients with ADHD in New Zealand, a therapeutic trial was conducted on 80 patients, with a reported 27% prevalence rate of vitamin D deficiency among patients. Vitamin D supplementation for 8 weeks resulted in alleviating most of the clinical manifestations of the disease. However, the addition of other micronutrients such as vitamin B12, zinc, iron, or folate was found to be ineffective.[37] Our findings are in agreement with a recently published Iranian randomized, double-blind, placebo-controlled trial in which supplementation with vitamin D at a dose of 2000 IU for 8 weeks as adjunctive therapy improved evening symptoms of ADHD.[38]

In a prospective cohort study in children, the authors did not support the theory of relationship between vitamin D levels and behavioral problems.[39] Further studies to elucidate the effect of vitamin D supplementation as monotherapy (without methylphenidate) on ADHD symptoms are recommended.

The authors found adverse effects of vitamin D supplementation in 15% of the patients in the form of mild abdominal pain, loss of appetite, or diarrhea. This is consistent with the findings of Otten et al[40] who concluded that oral vitamin D supplementation can cause mild adverse effects. The use of methylphenidate in conjunction with vitamin D administration can be considered a limitation in this study because the adverse effects of methylphenidate could mask those of vitamin D. Therefore, it may be difficult to attribute the reported adverse effects solely to vitamin D therapy.

Because of the small sample size of this study, a weak association between ADHD with vitamin D deficiency could not be excluded. Other limitations of our study included that we did not proceed for calculation of sample size or power of the study because data on the effect of vitamin D supplementation on ADHD symptoms are not sufficient for an exact calculation of statistical sample size.

The Conners' Parent Rating Scale is not a direct measure of the child's behavior, but a reflection of parental perception. It is subject to parental ability, time spent with the child, motivation for seeking treatment, and parents' tendency to be concerned about certain behaviors while overlooking others. These factors all have a significant impact on the resulting scores. Although the attrition rates did not reach conventional levels of significance in our study, the imbalance of data may still bias the study results.

Conclusion

We can conclude that children with ADHD had statistically greater vitamin D deficiency. This information highlights the importance of regular monitoring of serum levels of vitamin D and subsequent treatment of patients with vitamin D deficiency. This study provides preliminary evidence to suggest that vitamin D supplementation may improve aspects of cognitive functioning related to an ADHD diagnosis. Larger studies are required to further investigate the role of vitamin D in the pharmacological management of ADHD.

Acknowledgments

The authors offer many thanks to all nurses and residents in the pediatric department, Al Hada and Taif military hospitals for their effort in this work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Arns M, van der Heijden KB, Arnold LE, Kenemans JL. Geographic variation in the prevalence of attention-deficit/hyperactivity disorder: the sunny perspective. *Biol Psychiatry*. 2013;74:585-590. https://doi.org/10.1016/j.biopsych.2013.02.010. Accessed February 5, 2018.
2. Wehmeier PM, Schacht A, Barkley RA. Social and emotional impairment in children and adolescents with ADHD and the impact on quality of life. *J Adolesc Health*. 2010;46:209-217. https://doi.org/10.1016/j.jadohealth.2009.09.009. Accessed February 5, 2018.
3. Leroux JR, Turgay A, Quinn D. Advances in ADHD treatment. *Can J Diagn*. 2009;26:49-52.
4. Kemper KJ, Gardiner P, Birdee GS. Use of complementary and alternative medical therapies among youth with mental health concerns. *Acad Pediatr*. 2013;13:540-545. https://doi.org/10.1016/j.acap.2013.05.001. Accessed February 5, 2018.
5. Eyles DW, Burne THJ, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Front Neuroendocrinol*. 2013;34:47-64. https://doi.org/10.1016/j.yfrne.2012.07.001. Accessed February 5, 2018.
6. Russell G, Ford T, Rosenberg R, Kelly S. The association of attention deficit hyperactivity disorder with socioeconomic disadvantage: alternative explanations and evidence. *J Child Psychol Psychiatry*. 2014;55:436-445. https://doi.org/10.1111/jcpp.12170. Accessed February 5, 2018.
7. Groves NJ, Kesby JP, Eyles DW, McGrath JJ, Mackay-Sim A, Burne TH. Adult vitamin D deficiency leads to behavioural and brain neurochemical alterations in C57BL/6J and BALB/c mice. *Behav Brain Res*. 2013;241:120-131. https://doi.org/10.1016/j.bbr.2012.12.001. Accessed February 5, 2018.
8. Vinh Quoc Luong K, Thi Hoang Nguyen L. Vitamin D and Parkinson's disease. *J Neurosci Res*. 2012;90:2227-2236. https://doi.org/10.1002/jnr.23115. Accessed February 5, 2018.
9. Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Front Neuroendocrinol*. 2013;34:47-64. https://doi.org/10.1016/j.yfrne.2012.07.001. Accessed February 5, 2018.
10. Gale CR, Robinson SM, Harvey NC, et al. Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr*. 2008;62:68-77. https://doi.org/10.1038/sj.ejcn.1602680. Accessed February 5, 2018.
11. Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics*. 2012;129:485-493. https://doi.org/10.1542/peds.2011-2644. Accessed February 5, 2018.
12. Liska D, Quinn S, Lukaczer D, Jones D, Lerman R. *Textbook of Clinical Nutrition: A Functional Approach*. 2nd ed. Washington, DC: Institute for Functional Medicine; 2004:171-172.

13. Ross AC, Taylor CL, Yaktine AL, del Valle HB. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011.
14. Ellison-Wright I, Ellison-Wright Z, Bullmore E. Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. *BMC Psychiatry*. 2008;8:51. https://doi.org/10.1186/1471-244X-8-51. Accessed February 5, 2018.
15. Mithal A, Wahl DA, Bonjour JP, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int*. 2009;20:1807-1820. https://doi.org/10.1007/s00198-009-0954-6. Accessed February 5, 2018.
16. Steinmetz JP, Brunner M, Loarer E, Houssemand C. Incomplete psychometric equivalence of scores obtained on the manual and the computer version of the Wisconsin Card Sorting Test? *Eur J Psychol Assess* 2010;22:199-202. https://doi.org/10.1037/a0017661. Accessed February 5, 2018.
17. Cui X, Pertile R, Liu P, Eyles DW. Vitamin D regulates tyrosine hydroxylase expression: N-cadherin a possible mediator. *Neuroscience*. 2015;304:90-100. https://doi.org/10.1016/j.neuroscience.2015.07.048. Accessed February 5, 2018.
18. Orme RP, Bhangal MS, Fricker RA. Calcitriol imparts neuroprotection in vitro to midbrain dopaminergic neurons by upregulating GDNF expression. *PLoS One*. 2013;8:e62040. https://doi.org/10.1371/journal.pone.0062040. Accessed February 5, 2018.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 2002.
20. Heaney RP. Defining deficiency of vitamin D. *Clin Lab Int*. 2010;34:16-19.
21. Heaney RP. Health is better at serum 25(OH)D above 30ng/ml. *J Steroid Biochem Mol Biol*. 2013;136:224-228. https://doi.org/10.1016/j.jsbmb.2012.09.032. Accessed February 5, 2018.
22. El-Sheikh M, Bishry Z, Sadek A. *Attention Deficit Hyperactivity Disorder: An Egyptian Deficit Hyperactivity Disorder. An Egyptian Study*. Cairo, Egypt: Ain Shams University Press; 2002.
23. Conners CK. Rating scales for use in drug studies with children. *Psychopharmacol Bulletin* (Special Issue on Children) 1973; 24:24-29.
24. Goldstein FC, Green RC. Assessment of problem solving and executive functions. In: Mapou RL, Spector J, eds. *Clinical Neuropsychological Assessment*. New York, NY: Plenum Press; 1995:49-81. https://doi.org/10.1007/978-1-4757-9709-1_3. Accessed February 5, 2018.
25. Melika L, Dar El-Nahda El-Masryia. *Wechsler Intelligenee Scale for Children: Arabic Version*. Cairo, Egypt:1984.
26. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911-1930. https://doi.org/10.1210/jc.2011-0385. Accessed February 5, 2018.
27. Kamal M, Bener A, Ehlayel MS. Is high prevalence of vitamin D deficiency a correlate for attention deficit hyperactivity disorder? *Atten Defic Hyperact Disord*. 2014;6:73-78. https://doi.org/10.1007/s12402-014-0130-5. Accessed February 5, 2018.
28. Goksugur SB, Tufan AE, Semiz M, et al. Vitamin D status in children with attention deficit hyperactivity disorder. *Pediatr Int*. 2014;56:515-519. https://doi.org/10.1111/ped.12286. Accessed February 5, 2018.
29. Sharif MR, Madani M, Tabatabaei F, Tabatabaee Z. The relationship between serum vitamin D level and attention deficit hyperactivity disorder. *Iran J Child Neurol*. 2015;9(4):48-53.
30. Shang-Guan LL, Zhao YR. Serum levels of 25-hydroxyvitamin D in children with attention deficit hyperactivity disorder. *Zhongguo Dang Dai Er Ke Za Zhi*. 2015;17:837-840.
31. Tolppanen AM, Sayers A, Fraser W, et al. The association of 25-hydroxyvitamin D3 and D2 with behavioural problems in childhood. *PLoS One*. 2012;7:e40097. https://doi.org/10.1371/journal.pone.0040097. Accessed February 5, 2018.
32. Strøm M, Halldorsson TI, Hansen S, et al. Vitamin D measured in maternal serum and offspring neurodevelopmental outcomes: a prospective study with long-term follow-up. *Ann Nutr Metab*. 2014;64:254-261. https://doi.org/10.1159/000365030. Accessed February 5, 2018.
33. Gustafsson P, Rylander L, Christian HL, et al. Vitamin D status at birth and future risk of attention deficit/hyperactivity disorder (ADHD). *PLoS One*. 2015;10:e0140164. https://doi.org/10.1371/journal.pone.0140164. Accessed February 5, 2018.
34. Rickel AU, Brown RT. *Attention-Deficit/Hyperactivity Disorder in Children and Adults*. Boston, MA: Hogrefe & Huber; 2007.
35. Bryan J, Osendarp S, Hughes D, Calvaresi E, Baghurst K, van Klinken JW. Nutrients for cognitive development in school-aged children. *Nutr Rev*. 2004;62:295-306. https://doi.org/10.1111/j.1753-4887.2004.tb00055.x. Accessed February 5, 2018.
36. El Baza F, AlShahawi H, Zahra S, Abdel Hakim R. Magnesium supplementation in children with attention deficit hyperactivity disorder. *Egypt J Med Hum Genet*. 2016; 17:63-70.
37. Rucklidge JJ, Johnstone J, Gorman B, Boggis A, Frampton CM. Moderators of treatment response in adults with ADHD treated with a vitamin-mineral supplement. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;50:163-171. https://doi.org/10.1016/j.pnpbp.2013.12.014. Accessed February 5, 2018.
38. Mohammadpour N, Jazayeri S, Tehrani-Doost M, et al. Effect of vitamin D supplementation as adjunctive therapy to methylphenidate on ADHD symptoms: a randomized, double blind, placebo-controlled trial [published online December 7, 2016]. *Nutr Neurosci*. doi:10.1080/1028415X.2016.1262097. https://doi.org/10.1080/1028415X.2016.1262097. Accessed February 5, 2018.
39. Tolppanen A-M, Sayers A, Fraser WD, Lewis G, Zammit S, Lawlor DA. The association of 25-hydroxyvitamin D3 and D2 with behavioural problems in childhood. *PLoS One*. 2012;7:e40097. doi:10.1371/journal.pone.0040097. https://doi.org/10.1371/journal.pone.0040097. Accessed February 5, 2018.
40. Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press; 2006.