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Original Article

Effects of Folic Acid on Appetite in Children with Attention Deficit Hyperactivity Disorder (ADHD) Treated with Methylphenidate: A Randomized Double-Blind Clinical Trial

CME Article

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Abstract

Background: The highly effective medications in treating attention deficit hyperactivity disorder (ADHD) symptoms are stimulants like methylphenidate. However, they have adverse effects like reduced appetite. We investigated the effects of folic acid on reduced appetite caused by the use of methylphenidate in children with ADHD.

Methods: This randomized double-blind clinical trial evaluated 70 outpatients, aged between 6 and 12 years, with a diagnosis of ADHD. The children were recruited from the Outpatient Child and Adolescent Psychiatric Clinic of Golestan Hospital (Ahwaz, Iran) between 2016 and 2017. The study subjects were randomly assigned to 2 groups: Group 1 received an average dose of methylphenidate (1 mg/kg) plus folic acid (5 mg/d) and Group 2 received an average dose of methylphenidate (1 mg/kg) plus a placebo (5 mg of sucrose) for 8 weeks. Assessments, comprising the Conners Parent Questionnaire, anthropometric measurements, and appetite questionnaire, were conducted by a psychiatrist at baseline and then at 2, 4, 6, and 8 weeks after the medication was started using repeated measure analysis. The data were analyzed with the Mann–Whitney *U* and ANOVA tests using the SPSS statistical software (v. 18.0).

Results: Age and gender were not associated with the groups. Weight, height, and the body mass index were not changed during the study in both groups. ADHD symptoms significantly decreased in both groups during the trial; however, no difference was observed between the groups. Moreover, appetite was significantly improved in Group 1. Both medications were well tolerated.

Conclusion: It seems that folic acid improved the reduced appetite caused by the use of methylphenidate in our children with ADHD.

Trial Registration Number: IRCT2016040927304N1

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Keywords ● Attention deficit disorder with hyperactivity● Methylphenidate ● Folic acid● Clinical trial ● Appetite

What's Known

- One of the most pronounced mild adverse events in therapy with stimulants like methylphenidate is reduced appetite.
- Based on previous studies, some pediatricians in Iran prescribe folic acid empirically as an appetite-enhancer for low-weight children with poor appetite.

What's New

- This study showed that folic acid improved the reduced appetite caused by the use of methylphenidate in children with ADHD.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common lifelong neurobehavioral disorder and has an estimated prevalence

of 7.2% in school-aged children with serious consequences, including difficulties in family relationships, educational and occupational problems, and legal issues.[1-4]

According to guidelines, the current significant diagnostic criteria are based on the Diagnostic and Statistical Manual of Mental Disorders- 4th edition (DSM-IV) criteria, seeking coexisting conditions related to the diagnostic process and treatment and collecting information on the child's symptoms in more than 1 setting.[2,3]

The most common and highly effective medications in treating ADHD symptoms are stimulants such as methylphenidate and dextroamphetamine.[2,5] It has been reported that these drugs improve social behavior, neuropsychological functioning, and academic performance and confer long-term benefits in mental health.[6,7] Research has also revealed that therapy with stimulants, in addition to its effectiveness, is associated with common mild and rare serious adverse effects. According to previous studies, the most pronounced mild adverse events are insomnia and reduced appetite, with a respective frequency of 90% and 79%.[6,8]

Previous studies have demonstrated that poor appetite may lead to micronutrient deficiency, including iron or folic acid deficiency.[9] Folic acid exerts an effect on the synthesis of DNA and cell growth, particularly the cells of the gastrointestinal tract, where the synthesis and secretion of hormones such as peptide YY (PYY) that influence appetite are regulated.[9] Nonetheless, the mechanism of the impact of folic acid on appetite is still unclear.[9]

Based on previous studies, some pediatricians in Iran prescribe folic acid empirically as an appetite enhancer for low-weight children with poor appetite.[9] In their triple-blind clinical trial, Hatamizadeh et al.[10] investigated the effects of folic acid on the appetite of children between 3 and 5 years of age by administrating a 1 mg/day dose of folic acid for 20 days. In a cross-sectional study, Namdari et al.[9] determined the relationship between the level of folic acid and appetite status in children aged 3 to 6 years. The results of these investigations confirmed that folic acid was able to improve the appetite of preschool children with poor appetite.[9,10]

To the best of our knowledge, there is currently a dearth of studies evaluating the effects of folic acid on reduced appetite caused by the use of methylphenidate in children with ADHD.

In this randomized double-blind clinical trial, we aimed to investigate the effects of folic acid on reduced appetite caused by the use of methylphenidate in children aged between 6 and 12 years with ADHD by measuring changes in the appetite score, weight, and body mass index (BMI).

Patients and Methods

Ethical Consideration

An informed consent was obtained from the parents of the children prior to the commencement of the study. This study was approved by the Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (ethical approval code number: CT-P-9359-5679). The IRCT code of this study was IRCT2016040927304N1.

Participants

This randomized double-blind clinical trial recruited 70 outpatients, aged between 6 and 12 years, from the Outpatient Child and Adolescent Psychiatric Clinic of Golestan Hospital (Ahwaz, Iran) between 2016 and 2017. All the participants were diagnosed as ADHD children. As the prevalence of ADHD is approximately 7% and with a 95% confidence level and a margin of error of 0.05, it was estimated that a sample of 70 participants (35 children in each group) was needed.

Diagnostic Instruments

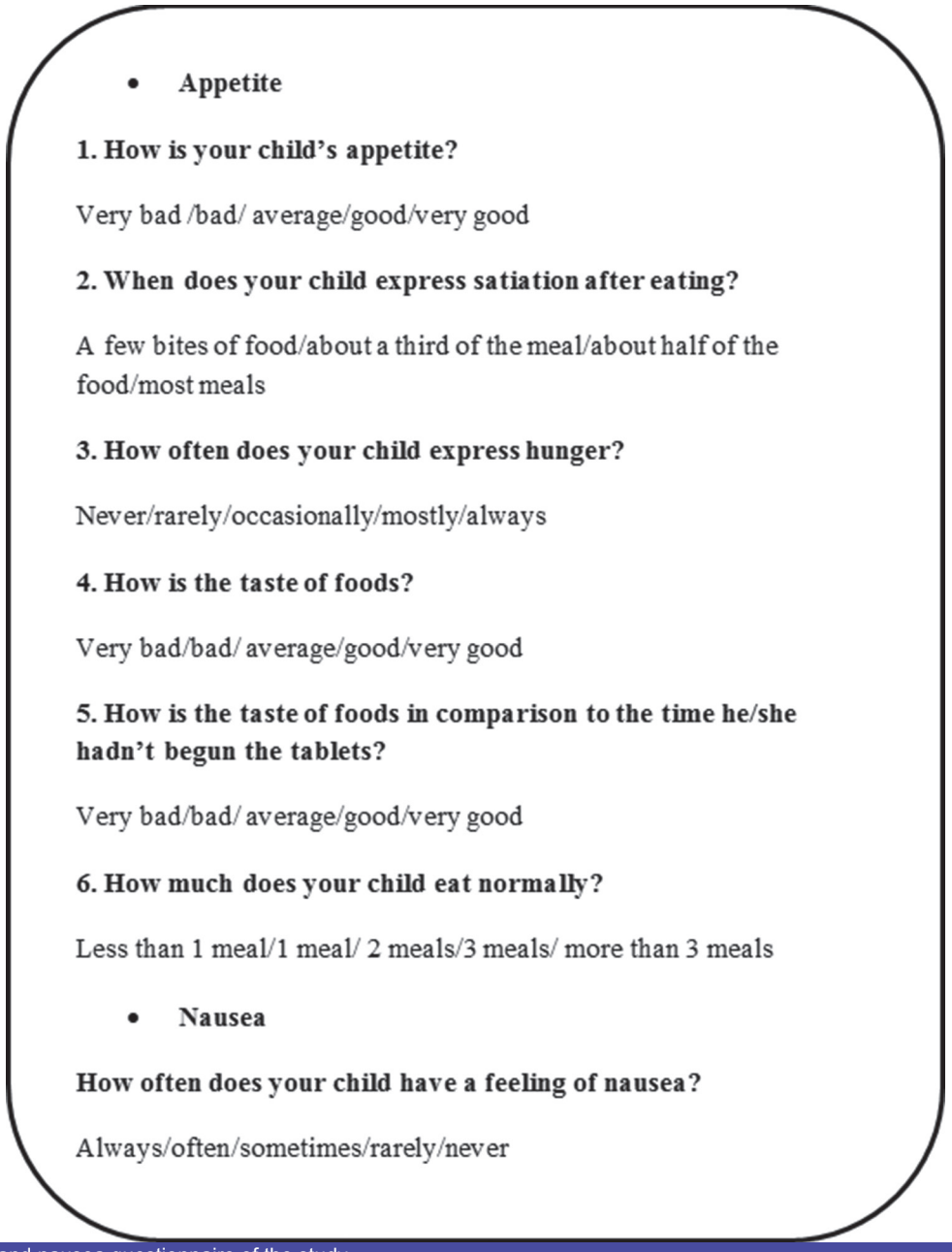
ADHD was diagnosed according to the DSM-IV diagnostic criteria. Eligibility for inclusion was approved by 2 board-certified child and adolescent psychiatrist and psychiatric specialist before the study.

Efficacy Measures

The Conners Parent Questionnaire was used to evaluate response to treatment in the patients with ADHD. This questionnaire has 26 questions and a rating scale between 26 and 104. A scale more than 34 represents attention deficit hyperactivity. The validity and reliability of this questionnaire are 85% and 91%, respectively.[11]

Anthropometric measurements were taken by psychiatry residents using standardized methods. Body weight was measured for each child to the nearest 0.1 kg. Height was measured with an accuracy of 0.1 cm. The BMI was calculated as weight in kilogram divided by the square of height in meters (kg/m^2). Demographic characteristics were obtained by interviewing the parents at enrollment in the study.

The children's appetite was assessed using the Council on Nutrition Appetite Questionnaire by asking their mothers 6 questions (figure 1).[12] The questionnaire has sensitivity and specificity of 82.7% and 71.7%, correspondingly, and validity and reliability of 60% and 47%, respectively.[12] A



- **Appetite**

1. How is your child's appetite?

Very bad /bad/ average/good/very good

2. When does your child express satiation after eating?

A few bites of food/about a third of the meal/about half of the food/most meals

3. How often does your child express hunger?

Never/rarely/occasionally/mostly/always

4. How is the taste of foods?

Very bad/bad/ average/good/very good

5. How is the taste of foods in comparison to the time he/she hadn't begun the tablets?

Very bad/bad/ average/good/very good

6. How much does your child eat normally?

Less than 1 meal/1 meal/ 2 meals/3 meals/ more than 3 meals

- **Nausea**

How often does your child have a feeling of nausea?

Always/often/sometimes/rarely/never

Figure 1: Appetite and nausea questionnaire of the study.

rating scale (6–30) was employed to rate the degree of appetite. The scales between 8 and 16, 17 and 28, and higher than 28 correspondingly represent the risk of low appetite, need for more investigation, and absence of appetite-related problems.

Nausea was assessed by asking the mothers to answer some related questions (figure 1). A rating scale between 1 and 5 was applied for each question. A higher score represents the better condition of the children in terms of nausea.

Procedure

The randomization and allocation process was done. All the study subjects were randomly assigned at a 1:1 ratio using a computer-generated code to receive either folic acid (5 mg/d) or a placebo. The patients were randomized to receive treatment with an average dose of methylphenidate (1 mg/kg) plus folic acid (5 mg/d) (Group 1) or an average dose of methylphenidate (1 mg/kg) plus the placebo (magnesium stearate, lactose, starch, sorbitol, and Avicel®) (Group 2) for an 8-week double-blind clinical trial. During the study period, the person who administrated the medications, the rater, and the patients were blinded to the treatment group. The assignments were kept in sealed, opaque envelopes until the point of allocation.

The inclusion criteria comprised age between 6 and 12 years, ADHD diagnosis based on the DSM-IV, clinical need to treat with methylphenidate, nonuse of other pharmacological interventions 2 weeks before the intervention, completing the consent form, and ability to refer for follow-up visits. Patients were excluded if they had epilepsy, diabetes, cardiovascular disorders, bipolar disorder, use of drugs that elevate the sympathetic system activity and cause conditions such as pheochromocytoma, using pseudoephedrine, psychosis in oneself or one's parents, use of any drugs and supplements which affect weight, low birth weight, history of prematurity, comorbid Tourette's syndrome, celiac disease, phenylketonuria, autism, mental retardation syndrome, failure to thrive confirmed in advance by pediatricians, history of severe side effects with the previous use of methylphenidate, drug-using mother, reduced appetite before the study, and minor thalassemia.

Assessments, with the aid of the Conners Parent Questionnaire, anthropometric measurements, and appetite questionnaire, were conducted by a psychiatrist at baseline and thereafter at 2, 4, 6, and 8 weeks after the commencement of the medication. Additionally, the side effect (nausea) was recorded during the study and was assessed using a checklist administered by a resident of psychiatry at weeks 2, 4, 6, and 8.

Data Analysis

The data were accumulated, analyzed, and presented as mean and standard deviation (mean±SD). In addition, the statistical comparisons between the groups were executed using the SPSS statistical software (v. 18.0). The Mann–Whitney *U* test was employed in order to compare age, weight, height, BMI, Conners Parent Scale, appetite score, and nausea score during the trial between the 2 groups. Repeated measures analysis of variance (ANOVA) was used to compare the effects of the interventions on the measurements at all 5 time points. A P≤0.05 was considered statistically significant.

Results

Out of the 70 children with ADHD, 66 patients met the inclusion criteria and agreed to participate in the study. They were randomly allocated to 2 groups. From the 33 children in each group, 2 patients from Group 1 and 4 patients from Group 2 dropped out in the 2nd week. In figure 2, the number of the patients assessed vis-à-vis their ADHD symptoms, the number of the patients who were randomly allocated to the 2 groups and completed the trial, and the number of the patients who withdrew from the study and the reasons for the withdrawals are presented. Finally the patients who completed the trial were analyzed.

All the measured characteristics of the participants in both groups such as sex, age, weight, height, BMI, and Conners Parent Scale at baseline are shown in table 1.

The percentage of girls in Group 1 and Group 2 was 32% and 28%, respectively. The mean age of the children in Group 1 and Group 2 was 8.13 and 8.24, correspondingly. The mean weight, height, and BMI of the cases were not significantly different between the groups, which showed the similarity of the patients in both groups before intervention. The mean Conners Parent Scale at baseline was 82.39 in Group 1 and 85.90 in Group 2. Based on table 1, the participants in both groups were statistically the same and comparable.

As is shown in table 2, the mean changes in weight, height, BMI, and Conners Parent Scale in both groups at baseline and at weeks 2, 4, 6, and 8 were not statically significantly different between the groups. Also, theses assessments were not significantly changed during the study period.

The test showed no statistically significant differences between the 2 groups regarding weight, height, BMI, Conners Parent Scale, and nausea, while there was a significant difference as regards the appetite score. Moreover, while time had no significant effect on weight, height, and the BMI, it had an impact on the Conners Parent Scale, appetite score, and nausea. Also, the results showed a significant time×group interaction in terms of weight, BMI, and appetite score. However, no significant time×group interaction was demonstrated in terms of height, Conners Parent Scale, and nausea.

According to table 3, the appetite score was not statically different between the groups at

Table 1: Characteristics of the patients in both groups at baseline

	Group 1	Group 2	P value
Sex			
Female	10 (32%)	8 (28%)	0.782
Male	21 (68%)	21 (72%)	
Age (y±SD)	8.13±1.38	8.24±2.18	0.814
Weight (kg)	28.31±5.19	27.97±6.41	0.821
Height (cm)	120.24±7.66	120.22±10.23	0.994
BMI	19.47±2.14	19.20±1.60	0.558
Conners parent scale	82.39±11.28	85.90±8.73	0.185

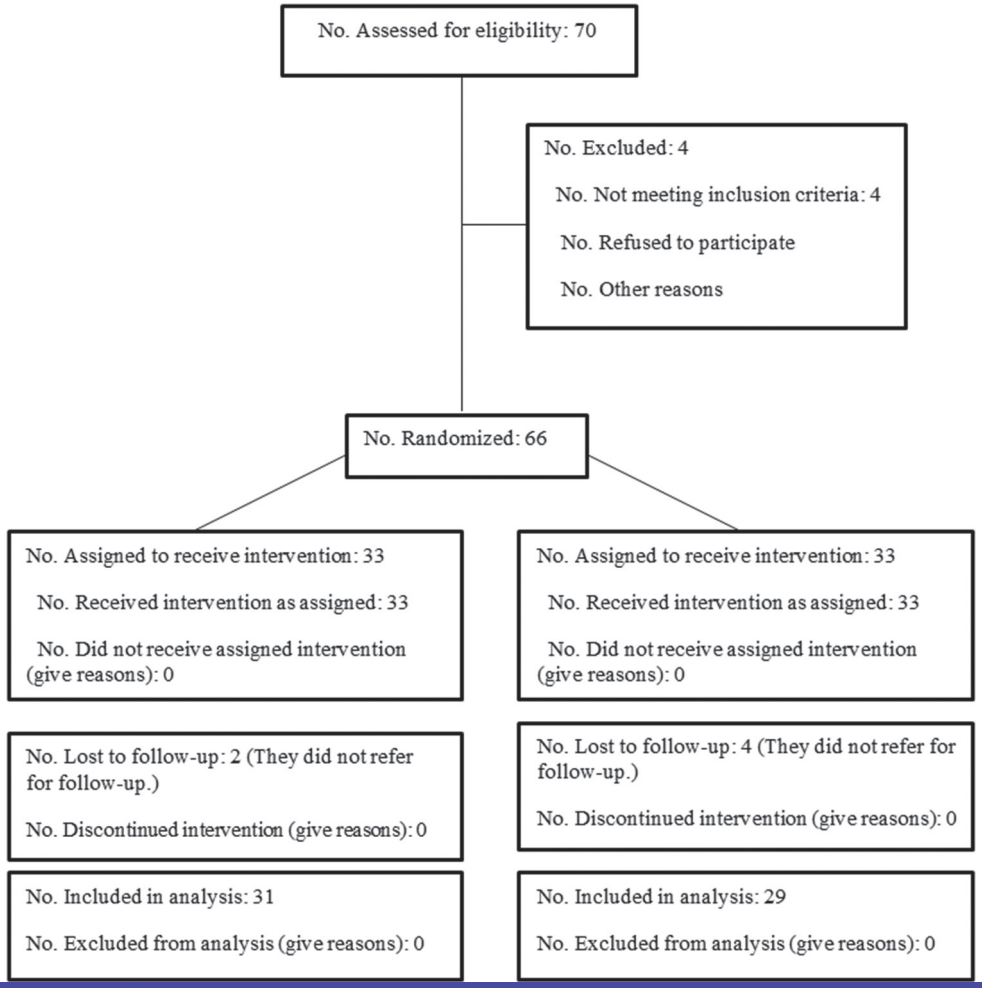


Figure 2: Participant's CONSORT flow diagram.

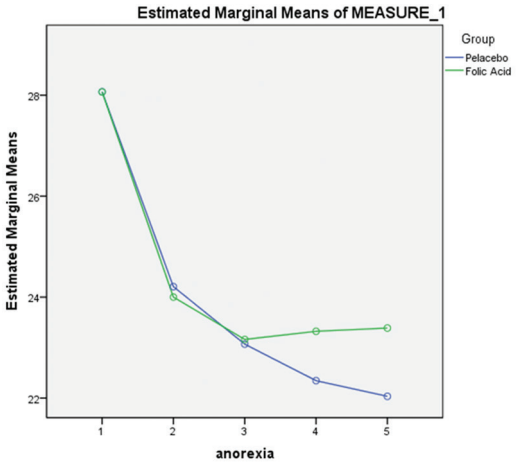


Figure 3: Comparison of appetite between the 2 groups during the study period. Horizontal axis represents time during the study period as: 1) baseline, 2) week 2, 3) week 4, 4) week 6, and 5) week 8.

baseline and at week 2. The difference in the appetite score was statically significant between the groups at weeks 6 and 8. As is depicted in figure 3, there was a decrease with an almost similar slope until week 4 in both groups. After week 4, appetite continued to drop with a lower slope in Group 2, whereas a rise was seen in Group 1.

The nausea scores of the children are presented in table 4. These data concerning nausea exhibited no significant changes between the groups during the trial. In other words, the patients were stable in terms of nausea during the study period.

Discussion

As is stated in previous studies, ADHD is strongly associated with lower levels of folate.[13] Moreover, higher hyperactivity problems are allied to lower maternal folate red blood cells.[14] On the other hand, several previous studies have demonstrated that the stop-signal reaction time (SSRT) tends to become longer in children with ADHD and that methylphenidate and other stimulants play a significant role in enhancing it; nonetheless, research has also shown that they have some side effects such as insomnia and decreased appetite.[15]

Table 2: Comparison of the changes in weight, height, BMI, and Conners Parent Scale between the 2 groups at baseline and at weeks 2, 4, 6, and 8

Group	Weight		P value	Height		P value	BMI		P value	Conners parent scale		P value
	1	2		1	2		1	2		1	2	
Baseline	28.31±5.19	27.97±6.41	0.821	120.24±7.66	120.22±10.23	0.994	19.47±2.14	19.20±1.60	0.558	82.39±11.28	85.90±8.73	0.185
Week 2	28.32±5.21	27.90±6.28	0.775	120.53±8.09	120.53±10.45	0.999	19.50±2.15	19.17±1.57	0.495	76.16±8.90	80.38±10.77	0.103
Week 4	28.40±5.26	27.85±6.30	0.710	120.57±8.11	120.53±10.45	0.990	19.54±2.14	19.14±1.68	0.432	69.87±11.63	74.55±12.68	0.141
Week 6	28.55±5.30	27.52±6.25	0.493	120.60±8.10	120.53±10.45	0.980	19.61±2.13	18.91±1.75	0.174	61.87±10.60	67.45±14.44	0.092
Week 8	28.63±5.30	27.48±6.22	0.445	120.61±8.10	120.53±10.45	0.974	19.66±2.11	18.91±1.78	0.144	56.45±11.11	60.72±13.38	0.183
Between-group difference	F (1, 58)=0.221		0.640	F (1, 58)=0.00		0.988	F (1, 58)=0.976		0.327	F (1, 58)=2.785		0.101

BMI: Body mass index

Folic acid supplementation can be useful in improving appetite and increasing food intake in children.[9] Appetite improvement is likely to induce feeling of hunger, which can be contributed to better growth in children.[9] In addition, folic acid influences the synthesis of DNA and cell growth, principally the gastrointestinal tract cells, in which the synthesis and secretion of hormones such as PYY that have some bearing on appetite are regulated. However, the mechanism whereby supplemental folic acid augments appetite has not been clearly delineated.[9] Although investigators have previously probed into the efficacy of folic acid in improving quality of life and reducing aggression and its symptoms in preschool children with ADHD, there is a dearth of data in the existing literature on the efficacy of folic acid in appetite improvement.

Kishnani et al.[16] presented a case of glycogen storage disease type Ib in an adolescent patient. He was in a good metabolic control and referred with poor appetite, weakness, depression, and vomiting of 3 months' duration. Extensive work-up demonstrated that the patient had B12, folate, iron, and other nutritional deficiencies. He showed symptom improvement after receiving therapeutic doses of deficient micronutrients. The authors followed up the patient for 2 months.

Nail et al.[17] studied in the laboratory the effects of the deletion of water-soluble (thiamin, riboflavin, pyridoxine, cyanocobalamin, pantothenic acid, folic acid, niacin, biotin, choline, inositol, and ascorbic acid) and fat-soluble (A, D, E, and K) vitamins on the growth and survival of juvenile shrimp for 8 weeks. They observed that diets deficient in folic acid resulted in poor appetite and poorer feed efficiency and there were histological changes in the digestive gland cells.

Kanani et al.[18] investigated the effects of iron-folic acid (IFA) supplements on hemoglobin, hunger, and growth in adolescent girls aged between 10 and 18 years in India. Their results showed increasing levels of hemoglobin, food intake, and weight gain in groups of girls who received IFA supplements, whereas hemoglobin decreased slightly and little weight gain was reported in the girls in the control group. The authors concluded that IFA supplementation was able to promote growth in underweight adolescents.

Hatamizadeh et al.[10] conducted a randomized triple-blind clinical trial to determine the effects of folic acid on the appetite of preschool children, between 3 and 5 years old, with poor appetite. According to their results, the children's appetite improved after receiving folic acid on the 20th day. Similar results were reported in a cross-sectional

Table 3: Comparison of the changes in appetite between the 2 groups at baseline at weeks 2, 4, 6, and 8

	Group	Baseline	P value	Week 2	P value	Week 4	P value	Week 6	P value	Week 8	P value	Between-group difference
Anorexia	1	28.06±0.25	0.946	24.00±1.37	0.564	23.16±0.97	0.552	23.32±0.91	<0.001	23.39±0.84	<0.001	F=13.173
	2	28.07±0.26		24.21±1.40		23.07±1.31		22.34±1.37		22.03±1.43		P=0.001

Table 4: Comparison of nausea between the 2 groups at baseline and weeks 2, 4, 6, and 8

	Group	Baseline	P value	Week 2	P value	Week 4	P value	Week 6	P value	Week 8	P value	Between-group difference
Nausea	1	4.35±0.76	0.909	4.03±0.84	0.762	4.00±0.86	0.085	3.84±0.93	0.733	4.03±0.75	0.328	F (1, 58)=0.633
	2	4.38±0.90		3.97±0.87		3.62±0.82		3.76±0.87		3.83±0.85		P=0.430

study that aimed to assess the effects of folic acid on the appetite of preschool children, between 3 and 6 years of age. Based on this study, a positive association was detected between the levels of serum folate and improved appetite.[9]

In a randomized double-blind placebo-controlled clinical trial, Ghanizadeh et al.[1] examined the efficacy of methylphenidate with folic acid in improving quality of life and treating aggression and ADHD symptoms in children with ADHD. The investigators concluded that methylphenidate might improve ADHD symptoms and the quality of life of children with ADHD. Their evidence, however, failed to support the efficacy of folic acid in treating ADHD symptoms or aggression or in improving quality of life in children with ADHD.

Accordingly, there is a paucity of studies evaluating the relationship between acid folic and appetite level, especially in children with ADHD. The present study is one of the 1st randomized, double-blind, placebo-controlled trials to evaluate the effects of folic acid on appetite in children with ADHD, aged between 6 and 12 years. Even so, first and foremost among the limitations in the present study is the absence of laboratory data and follow-up of the patients after the 8-week study period.

The results of the current study showed that folic acid was able to enhance the diminished appetite in consequence of the use of methylphenidate in children with ADHD aged between 6 and 12 years. We also found that despite the significant improvement in appetite, no significant change in weight gain was demonstrated. It is worthy of note that folic acid was well tolerated in our cases and no adverse effects such as nausea were reported in the folic acid group. These results seem to be in line with previous studies.

Finally, we suggest that further studies incorporating laboratory data changes such as peripheral blood smear and glucose, lipid, protein, and serum folic acid levels be undertaken for a more in-depth assessment of the effects of folic acid on appetite in children with ADHD. In addition, as the duration of the present study was approximately short (8 weeks), it seems advisable that the long-term effects and safety of folic acid be investigated in larger groups of participants.

Conclusion

Folic acid was able to improve the reduced appetite caused by the use of methylphenidate in children with ADHD aged between 6 and 12 years.

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Conflict of Interest: None declared.

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