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Original Article

Folic acid and zinc serum levels in pediatric patients with cystic fibrosis

Hassan Talakesh[1], **Karamali Kasiri**[1*], **Fatemeh Deris**[2], **Aigin Houshang**[3]

[1]Department of Pediatrics, Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2]Department of Epidemiology and Biostatistics, School of Health, Shahrekord University of Medical Sciences, Shahrekord, Iran
[3]Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran

*Corresponding Author: Karamali Kasiri, Email: kasiri207@yahoo.com

Abstract

Background and aims: Folic acid and zinc (Zn) levels in children with cystic fibrosis (CF) have not been studied further in previous studies Due to limited information about Iranian children, the present study was conducted to assess serum levels of folic acid and Zn in children with CF in the city of Shahrekord.

Methods: The present case-control study compared 20 children with CF, referring to Hazrat Rasoul Shahrekord Clinic as the case group and 20 children without CF as the control group. The serum Zn and folic acid levels were determined for both groups using blood samples, and the data were analyzed in SPSS v18 software.

Results: The mean serum level of folic acid and the Zn level were 12.42 ± 5.66 and 92.45 ± 24.70 in the case group, as well as 16.81 ± 2.31 and 107.13 ± 6.44 in the control group. There was a significant difference between the serum level of folic acid ($P = 0.004$) and the serum level of Zn ($P = 0.014$) between the two groups. Zn deficiency was observed in five children (25%) in the case group but in none of the control children ($P = 0.047$). No significant difference was found in folic acid deficiency between the groups ($P > 0.99$).

Conclusion: Children with CF had lower serum levels of folic acid and Zn than children without CF. The incidence of Zn deficiency in CF children was likely due to limited access to PERT.

Keywords: Cystic fibrosis, Folic acid, Zinc, Children

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Introduction

Cystic fibrosis (CF) is the most common autosomal disease that restricts life. The disease is caused by the reduced transmission of chloride ions across the lateral plasma membrane of vertebrate epithelial cells (1). It can also result in complications with symptoms, including a saline taste, growth failure despite adequate nourishment, digestive problems, intestinal obstruction, concentrated mucosal accumulation, recurrent lung infection, cough, and shortness of breath. It has been defined as the most prevalent life-threatening inherited disorder in children (2). CF is the second most common cause of exocrine pancreatic insufficiency (EPI) after chronic pancreatitis (3). Malnutrition is associated with poorer overall health, more severe pulmonary disease, and shorter life expectancy in children with CF and adults (4-6). International nutrition guidelines for patients with CF emphasize three principles, namely, energy intake, pancreatic enzyme replacement therapy (PERT), and the consumption of fat-soluble vitamin supplements (7).

Unlike fat-soluble vitamins, there is no specific recommendation for patients with CF for water-soluble vitamins, possibly due to the perception and some evidence that CF patients undergoing PERT and consuming a well-balanced diet do not manifest overt deficiencies (8). However, evidence exists that patients with EPI have a higher risk of zinc (Zn) deficiency (9). It has been observed that infants with CF experience Zn deficiency prior to the initiation of PERT because of malabsorption and increased excretion of endogenous Zn (10). Furthermore, complications such as liver disease, malabsorption, and improper medication use can impair CF patients' receipt of water-soluble vitamins such as folic acid (Vitamin B9) (11).

Most studies on the nutritional status of patients with CF and their serum levels of vitamins and micronutrients have been conducted in developed Western nations. None have been performed in developing countries. Additionally, unlike fat-soluble vitamins, there is no specific recommendation for the consumption of folic acid and Zn supplements in the treatment regimen of patients with CF. They have received less attention, and their levels should be monitored (12). PERT indirectly improves fat malabsorption, which has been shown to improve the incidence of digestive disorders, protein and calorie malnutrition, and fatty diarrhea in CF patients

(13). Iranian patients with CF currently have limited access to PERT. As a result, the present study was designed to determine the serum levels of folic acid and Zn in children with CF aged six months to 14 years in Shahrekord.

Materials and Methods

This case-control study was conducted on children aged six months to 14 years in control and CF groups selected using the convenience sampling method. The disease was confirmed by genetic testing for CFTR gene mutation, sweat tests, and clinical findings, and the appropriate treatments were administered under the supervision of a pediatric gastroenterologist.

The control group consisted of children and adolescents without CF who had been referred to the Hazrat Rasool Shahrekord Clinic with chronic abdominal pain. The subjects in the control group were matched with those in the case group in terms of age and gender. According to previous studies, the sample size was calculated to be 20 individuals for each group using the sample size formula (14). The groups were matched based on age and gender-matched controls and group matching.

After receiving written consent from their parents, the participants were enrolled in the study. Their parents filled out questionnaires that contained demographic and clinical data about the age, gender, and CF status of the children. Blood samples were then taken from these subjects by the reference laboratory of Shahrekord University of Medical Sciences, and the serum levels of Zn and folic acid were determined.

Flame atomic absorption spectrometry, which has high sensitivity and specificity, was used to measure the serum Zn levels. In this method, 5 cc of venous blood was taken from the subject and kept for 30 minutes in a metal-free tube (plastic vial) until the sample had clotted. The clot was centrifuged for 15 minutes at 2500-3000 rpm, and then the serum was separated from the cellular fraction. The atomic absorption spectrometry device was then utilized to determine the Zn level.

To measure the serum level of folic acid, 5 cc of venous blood was taken from the subject using the immunoassay method. The sample was not lysed or exposed to direct light. The blood sample was centrifuged for 15 minutes at 2500-3000 rpm, and then the serum was separated into special tubes to determine the level of folic acid. The gathered data were entered into the SPSS v18 statistical software and analyzed with descriptive (frequencies, percentages, means, and standard deviations) and analytical (Chi-square test, independent t-test, and Pearson's correlation coefficient) statistics. A level of $P<0.05$ was considered statistically significant.

Results

This study comprised 20 children with CF as the case group and 20 without CF as the control group. The groups were gender-matched, as the case group consisted of 8 girls and 12 boys, and the control group contained 9 girls and 11 boys ($P>0.99$). There was no significant difference in the mean age between the groups ($P>0.99$, Table 1).

Based on the results (Table 2), the case group's mean serum level of folic acid (12.42 ± 5.66) was significantly lower than that of the control group (16.81 ± 2.31, $P=0.004$). In addition, the case group's Zn serum level (92.45 ± 24.70) was significantly lower than that of the control group (107.13 ± 6.44, $P=0.004$).

The results demonstrated no significant linear correlation between age and serum levels of folic acid ($P=0.596$, $r=0.126$) and Zn ($P=0.334$, $r=0.228$) in the control group. There also was no significant linear correlation between age and serum levels of folic acid ($P=0.996$, $r=0.001$) and Zn ($P=0.408$, $r=0.196$) in the case group.

The findings (Table 3) revealed that there was no significant difference between groups in terms of folic acid deficiency ($P>0.99$). Five children (25%) in the case group had Zn deficiency, but none of those in the control group suffered from Zn deficiency, highlighting a significant difference between the groups ($P=0.047$).

Discussion

The study findings revealed that children with CF in the case group had significantly lower serum levels of Zn (92.45 ± 24.70) in comparison to children in the control group (107.13 ± 6.44). Additionally, five children in the case group (25%) had Zn deficiency compared to none in the control group, and statistical analysis showed a significant difference between the two groups. In line with the current study, Yadav et al (15) found that significantly more children with CF in the case group had Zn deficiency compared to the control group (96% vs. 11%). In this study, only 22.2% of patients received PERT, probably the

Table 1. Gender frequency distribution and mean age in two groups

Variable		Case group	Control group	*P* value
Gender	Male: N (%)	12 (60%)	11 (55%)	>0.99
	Female: N (%)	8 (40%)	9 (45%)	
Mean age ± SD		7.45 ± 4.54	7.45 ± 4.00	>0.99

Note. SD: Standard deviation.

Table 2. Mean levels of folic acid and zinc in two groups

Variable	Case group (Mean ± SD)	Control group (Mean ± SD)	*P* value
Serum level of folic acid	12.42 ± 5.66	16.81 ± 2.31	0.004*
Serum level of zinc	92.45 ± 24.70	107.13 ± 6.44	0.014*

Note. *$P<0.05$. SD: Standard deviation.

Table 3. Zinc and folic acid deficiency by group

Variable			Case group n (%)	Control group n (%)	*P* value
Serum level of folic acid	Deficiency	Yes	1 (5)	0 (0)	>0.99
		No	19 (95)	20 (100)	
Serum level of zinc	Deficiency	Yes	5 (25)	0 (0)	0.047*
		No	15 (75)	20 (100)	

Note. *$P<0.05$.

reason for the high prevalence of Zn deficiency in the case group. The findings of a study demonstrated that since 94% of CF patients had a Cu/Zn ratio above 1, this fact should warn us of the possibility of Zn deficiency and a high inflammatory response. One's Zn status cannot be determined solely by the serum Zn measurement. However, the Cu/Zn ratio in CF patients might indicate inflammation and Zn deficiency (16).

A previous observation from the Colorado Newborn Screening Program indicated that the Zn status was frequently less than optimal in infants with CF at 6 weeks. Approximately 30% of patients had plasma Zn concentrations that were less than normal, indicating medium Zn deficiency (17). Treatment with pancreatic enzymes was associated with significantly increasing plasma concentrations in the same infants. Another cross-sectional study (18) showed that 22.4% of patients with CF had low plasma concentrations (< 9.2 µmol/L), which conforms to the findings of the current study.

In another study on infants with CF (19), the mean dietary Zn absorption was significantly lower than that of healthy infants. Additionally, the absolute amount of endogenous Zn was about 50% higher than the values found in healthy infants, and there was a positive correlation between endogenous Zn excretion in stool and fecal fat excretion, indicating Zn deficiency. Armstrong et al (20) reported similar findings regarding patients with severe EPI.

In contrast to the above-mentioned studies that suggest that patients with CF and EPI had Zn deficiencies (especially patients who had not undergone PERT), a cross-sectional study performed by Lloyd-Still and Ganther (21) on 13 children with CF and EPI who had all undergone PERT and another study by Kelleher et al (22) on patients with CF reported no correlation between EPI and Zn status. The difference in their findings may be related to demographic variations, dietary preferences of the patients, and/or compliance with PERT guidelines. However, most studies have demonstrated Zn deficiency in patients with CF and EPI. A systematic review of 13 studies found a significant correlation between EPI and Zn status, and it has been suggested that further studies should be performed before recommending the routine use of Zn supplements in these children (9).

The findings of our study also confirmed that the mean serum level of folic acid in the case group (12.42 ± 5.66) was significantly lower than in the control group (16.81 ± 2.31). However, there was no statistically significant difference in folic acid deficiency between the case and control groups (5% vs. 0%), which is likely due to the small sample size, and more studies are suggested in this regard. Thus far, the few studies that have focused on the deficiency of group B vitamins, including folate, in CF patients have reported similar results.

Dietary modifications will probably become more variable in the future because, on the one end of the spectrum, some patients who are ineligible for highly effective modulator therapies (HEMT) or who continue to be malnourished or underweight despite HEMT will still require the traditional CF diet, while, on the other end of the spectrum, patients who become overweight or obese (more likely on HEMT) will need lower-calorie diets (23).

Conclusion

Children with CF were found to have lower serum levels of folic acid and Zn than the non-CF control children. Zn deficiency was more common in CF children, likely due to limited access to PERT therapy. This emphasizes the importance of folic acid and Zn supplementation and the availability of PERT.

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Authors' Contribution

Conceptualization: Hassan Talakesh, Karamali Kasiri.
Data curation: Fatemeh Deris.
Formal analysis: Fatemeh Deris.
Funding acquisition: Karamali Kasiri.
Investigation: Aigin Houshang.
Methodology: Fatemeh Deris and Hassan Talakesh.
Project administration: Aigin Houshang.
Resources: Aigin Houshang.
Writing–original draft: Hassan Talakesh, Karamali Kasiri.
Writing–review & editing: Hassan Talakesh, Karamali Kasiri, Aigin Houshang, Fatemeh Deris.

Competing Interests

The authors declared there are no conflicts of interests.

Ethical Approval

The study protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1399.234). The case group was selected from among patients with CF who had been referred to Hazrat Rasool Shahrekord Clinic in 2021.

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