Effect of supplementary zinc on body mass index, pulmonary function and hospitalization in children with cystic fibrosis

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SUMMARY: Ataee P, Najafi M, Gharagozlou M, Aflatounian M, Mahmoudi M, Khodadad A, Farahmand F, Motamed F, Fallahi GH, Kalantari N, Soheili H, Modarresi V, Sabbaghian M, Rezaei N. Effect of supplementary zinc on body mass index, pulmonary function and hospitalization in children with cystic fibrosis. Turk J Pediatr 2014; 56: 127-132.

Zinc deficiency, which is common in patients with cystic fibrosis (CF), can lead to several complications that may increase the number of hospital admissions in this group of patients. As supplementary zinc can prevent such complications, this study was performed to evaluate the effect of supplementary zinc on body mass index (BMI), forced expiratory volume in one second (FEV1) and number of hospitalizations in CF patients.

In this study, 30 children with CF, who were referred to the Digestive Diseases Clinic of the Children's Medical Center in Tehran, were enrolled. Supplementary zinc of 2 mg/kg per day was administered to all patients. Serum level of zinc, alkaline phosphatase, and albumin as well as BMI, FEV1, and number of hospitalizations were compared before and after zinc administration.

Height ($p<0.001$), weight ($p<0.001$) and BMI ($p=0.001$) were significantly increased after zinc, while the number of hospitalizations was significantly decreased ($p=0.023$). In contrast to patients with normal pulmonary function tests who received supplement therapy, BMI was not increased in those with abnormal pulmonary function after supplementary zinc.

Supplementary zinc can increase BMI in CF patients, mostly in those with normal pulmonary function. While supplementary zinc may decrease the number of hospitalizations, other factors can also influence the hospitalization number.

Key words: cystic fibrosis, zinc deficiency, supplementary zinc, body mass index, pulmonary function test, hospitalization.

Cystic fibrosis (CF) seems to be the most common multisystem autosomal recessive disease, with a frequency of 1 in 2000-3000 live births, mainly characterized by obstruction and infection of airways and pancreatic insufficiency as the usual presenting manifestations of the disease[1-4].

With progression of disease, chronic bronchitis and dyspnea develop, and failure to gain weight, presented as decreased body mass index (BMI), appears[1,5]. The patients are usually hospitalized several times due to active airway infections for effective treatment[1]. Therefore, early determination of pulmonary dysfunction in CF patients is very important. Hyperinflation of the lung fields on chest radiograph and obstructive pattern in pulmonary function test (PFT) can show such complications of the disease[1,5]. Forced expiratory volume in one second (FEV1) is the key outcome measure in CF, which is routinely used to monitor the rate of lung disease progression, the need for additional interventions, and the effectiveness

of such interventions[6].

Appropriate treatment is necessary when a pulmonary disease is diagnosed. Chest physical therapy, bronchodilators, anti-inflammatory agents, and some other drugs such as DNAse for secretion clearance as well as nutritional therapy can be used during lung disease[1,7-9]. Patients with CF require dietary adjustments, pancreatic enzyme replacement, supplementary vitamins (vitamin A, D, E, and K), and supplementary essential trace elements due to pancreatic insufficiency and inadequate digestion and absorption of fats and proteins[1].

Zinc is an essential trace element, the intake of which is closely related to protein intake, and it is mostly absorbed in the small intestine[10]. Zinc is the intrinsic metal component or activating cofactor for more than 70 important enzyme systems, including carbonic anhydrase, alkaline phosphatases (ALP), dehydrogenases, and carboxypeptidases[10]. It is also an important element in the immune system and consequently in the response to pathogens[11].

In CF patients, zinc deficiency can be common due to disturbed protein intake and fat malabsorption[12]; low plasma zinc concentrations have been reported in approximately 30% of young infants with CF in newborn screenings[10,13-15]. Zinc deficiency can cause growth failure, primary hypogonadism, skin disease, impaired taste and smell, impaired immunity, and susceptibility to infections, which can increase the number of hospital admissions in affected patients[10,16]. As supplementary zinc can prevent these complications[10], administration of supplementary zinc to patients with CF may be beneficial[17-21].

Since zinc deficiency is common in the Iranian population due to the poor intake[22] and is a common deficiency in CF patients, a more profound zinc deficiency in Iranian CF patients is expected when compared to other countries. Therefore, we performed this study to evaluate the effect of supplementary zinc on BMI, FEV1 and the number of hospitalizations among CF patients.

Material and Methods

In this study, 30 children with CF, who were referred to the Digestive Diseases Clinic of the Children's Medical Center in Tehran, were investigated. Only patients who were older than four years with a confirmed diagnosis of CF were included. All the patients were under the treatment protocol of the hospital with pancreatic enzyme and vitamins A, D, and E supplements, vitamin K, salbutamol, and 5% saline nebulizer. After obtaining informed consent, a blood sample was taken, and the serum levels of zinc, ALP and albumin were measured.

The clinical data and results of laboratory tests were entered in the proposed questionnaire for this study. Clinical variables included sex, age, history of zinc usage, height, weight, BMI, and number of previous hospitalizations. Then, PFT was done to measure FEV1. Elemental zinc at a dose of 2 mg per kilogram per day was administered for six months. After this six-month period, another blood sample was taken to assess the same factors in the serum as with the first blood sample. Again, a questionnaire, with the same variables as gathered at the beginning of the study, was completed. PFT was also repeated to compare the new FEV1 with the first measurement.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical software (version 16). The data were analyzed using the paired Student t-test and McNemar test.

Results

In this study, 20 male and 10 female children with CF were included. Patients' ages ranged from 4 to 15 years old (mean age: 8.65±3.01 years). Twenty-three (76.7%) patients had a history of regular zinc consumption prior to the study. Other patients did not use zinc or used it irregularly.

Zinc, ALP, albumin, height, weight, BMI, and FEV1 were measured both before and after administration of the elemental zinc (Table I). Serum zinc level as well as ALP and albumin did not change significantly after administration of zinc when compared to baseline values. However, height, weight and BMI were significantly increased after the zinc administration.

Before the trial, the BMI of 9 (30%) patients was below the 5th percentile; BMI was between the 5th and 10th percentile in 4 (13.3%), 10th and 25th percentile in 11 (36.7%), 25th and 50th percentile in 4 (13.3%), 50th and 75th

Table I. Comparison of Variables Before and After Supplementary Zinc Administration in CF Patients

Variable	Before zinc usage	After zinc usage	P-value
Zinc (μg/ml)*	111.43±22.92	111.57±20.15	0.920
ALP (unit/L)*	700.70±218.77	688.87±174.04	0.382
Albumin (g/dl)*	4.42±0.64	4.53±0.59	0.313
Height (cm)	122.23±15.11	122.75±15.02	<0.001
Weight (kg)	22.08±6.81	22.44±6.74	<0.001
BMI (kg/m^2)	14.48±1.19	14.62±1.21	0.001
Hospitalization number (/year)	0.23±0.504	0.07±0.254	0.023
FEV1 (%)*	88.22±24.61	82.86±23.69	0.002

** Normal ranges: Zinc, 50-150 μg/ml; ALP, 180-1200 unit/L; Albumin, 3.5-5.2 g/dl; FEV1>80%.*
ALP: Alkaline phosphatase. BMI: Body mass index. FEV1: Forced expiratory volume in one second.

Table II. Comparison of the Results Before and After Supplementary Zinc Administration between Male and Female CF Patients

Variable	Males (20 cases)			Females (10 cases)		
	Before zinc use	After zinc use	P-value	Before zinc use	After zinc use	P-value
Zinc (μg/ml)*	104.15±22	104.55±19.88	0.808	126±17.79	125.60±12.06	0.871
ALP (unit/L)*	676.05±181.45	675±153.88	0.942	750±284	716.60±215.25	0.266
Albumin (g/dl)*	4.44±0.53	4.06±0.27	0.330	4.38±0.85	4.47±0.71	0.373
Height (cm)	124.72±14.36	125.17±14.18	0.001	117.90±16.22	117.25±19.10	0.002
Weight (kg)	23.42±6.81	23.76±6.69	<0.001	19.40±6.29	19.81±6.35	<0.001
BMI (kg/m^2)	14.79±1.17	14.93±1.23	0.013	13.87±1.03	14.01±0.96	0.054
Hospitalization number (/year)	0.30±0.571	0.05±0.224	0.021	0.1±0.316	0.1±0.316	1
FEV1 (%)*	88.69±28.38	82.40±26.37	0.008	87.29±15.83	83.80±18.40	0.121

* Normal ranges: Zinc, 50-150 μg/ml; ALP, 180-1200 unit/L; Albumin, 3.5-5.2 g/dl; FEV1>80%.
ALP: Alkaline phosphatase. BMI: Body mass index. FEV1: Forced expiratory volume in one second.

percentile in 1 (3.3%), and 85th and 90th percentile in 1 (3.3%). After administration of the elemental zinc, BMI of 8 (26.7%) patients was below the 5th percentile; BMI was between the 5th and 10th percentile in 5 (16.7%), 10th and 25th percentile in 9 (30.0%), 25th and 50th percentile in 3 (10.0%), 50th and 75th percentile in 4 (13.3%), and 85th and 90th percentile in 1 (3.3%). Although the number of cases with BMI between the 50th and 75th percentile was increased after therapy, there was no significant difference among these BMI categories in general (p=0.176).

Pulmonary function test (PFT) was normal in 19 (63.3%) patients before administration of the zinc, while obstructive, restrictive and mixed patterns were found in 2 (6.7%), 4 (13.3%), and 5 (16.7%) cases, respectively. Although patterns of PFTs were not changed in any patient after zinc therapy, mean FEV1 was significantly decreased (Table I).

Comparisons of the results between male and female subjects showed similar results as in the whole group, except for an insignificant difference in BMI, hospitalization number, and FEV1 of female subjects (Table II).

Comparisons of results were also done between patients with normal PFT and those with abnormal PFT. The only difference with the general comparison was the insignificant change in hospitalization number in both groups, insignificant change in BMI of patients with abnormal PFT, and FEV1 of patients with normal PFT (Table III).

The final comparisons of results were made

Table III. Comparisons of Results Before and After Supplementary Zinc Administration in CF Patients with Normal and Abnormal PFT

Variable	Patients with normal PFT			Patients with abnormal PFT		
	Before zinc use	After zinc use	P-value	Before zinc use	After zinc use	P-value
Zinc (μg/ml)*	107±21.83	110.42±18.82	0.124	119.09±23.73	113.55±23.09	0.08
ALP (unit/L)*	695.37±233.23	687.16±179.12	0.646	709.91±201.83	691.82±173.42	0.408
Albumin (g/dl)*	4.28±0.72	4.43±0.63	0.20	4.65±0.40	4.43±0.78	0.373
Height (cm)	121.18±15.24	121.71±15.15	<0.001	124.04±15.45	124.54±15.34	0.008
Weight (kg)	21.86±7.42	22.30±7.39	<0.001	22.45±5.93	22.68±5.78	0.034
BMI (kg/m^2)	14.54±1.22	14.71±1.25	0.004	14.39±1.19	14.47±1.19	0.175
Hospitalization number (/year)	0.21±0.535	0.05±0.229	0.083	0.27±0.467	0.09±0.302	0.167
FEV1 (%)*	100.08±15.08	95.89±11.41	0.086	67.73±24.87	60.36±22.66	0.001

* Normal ranges: Zinc, 50-150 μg/ml; ALP, 180-1200 unit/L; Albumin, 3.5-5.2 g/dl; FEV1>80%.
ALP: Alkaline phosphatase. BMI: Body mass index. FEV1: Forced expiratory volume in one second. PFT: Pulmonary function test.

Table IV. Comparison of Results Before and After Supplementary Zinc Administration in CF Patients Younger and Older than 10 years

Variable	Patients younger than 10 years			Patients older than 10 years		
	Before zinc use	After zinc use	P-value	Before zinc use	After zinc use	P-value
Zinc (μg/ml)*	119.09±23.73	113.55±23.09	0.08	112.78±17.25	111.78±19.62	0.728
ALP (unit/L)*	709.91±201.83	691.82±173.42	0.408	711.89±168.28	728.67±166.49	0.23
Albumin (g/dl)*	4.65±0.40	4.43±0.78	0.373	4.71±0.49	4.61±0.58	0.387
Height (cm)	124.04±15.45	124.54±15.34	0.008	141.27±10.68	141.55±10.87	0.095
Weight (kg)	22.45±5.93	22.68±6.78	0.034	30.11±6.96	30.28±6.96	0.078
BMI (kg/m^2)	14.39±1.19	14.47±1.19	0.175	14.86±1.47	14.91±1.48	0.362
Hospitalization number (/year)	0.27±0.467	0.09±0.302	0.167	0.11±0.33	0	0.347
FEV1 (%)*	67.73±24.87	60.36±22.66	0.001	74.14±30.44	68.88±31.60	0.123

* Normal ranges: Zinc, 50-150 μg/ml; ALP, 180-1200 unit/L; Albumin, 3.5-5.2 g/dl; FEV1>80%
ALP: Alkaline phosphatase. BMI: Body mass index. FEV1: Forced expiratory volume in one second.

between patients younger and older than 10 years. In contrast to the general comparison, height, weight, and FEV1 changes were only significant in patients younger than 10 years (Table IV).

Discussion

Zinc deficiency, a common problem in patients with CF, can lead to several complications that may increase the number of hospitalizations in this group of patients. As supplementary zinc can prevent such complications, this study was performed to evaluate the effect of supplementary zinc on BMI, FEV1 and number of hospitalizations in CF patients.

According to the results of this study, mean zinc level was 111.43 μg/dl, which is much higher than the cut-off point of 60 μg/dl[23]. Moreover, there was no significant difference in serum albumin or ALP levels before and after supplementary zinc administration. Although this result is in contrast to the

primary assumption of zinc deficiency as a common problem in CF patients, the conclusion is limited by the fact that more than 75% of the enrolled patients were under regular zinc consumption prior to the study. Further, plasma zinc measurements are relatively insensitive and mild zinc deficiency occurs with normal plasma levels[24,25]. In addition, in some previous studies, there was no significant difference in serum zinc concentration between CF patients and healthy controls[19,26,27], and zinc deficiency was not so common in CF patients[27,28]. On the other hand, zinc supplementation has been suggested both as a therapeutic agent and as a potential prophylactic agent in children in developing countries[29]. Thus, based on normal serum levels of zinc in Iranian patients with CF, we cannot suggest excluding zinc supplementation in the treatment of CF patients.

It should be noted that height and weight were improved after zinc administration in our study. Any conclusion from this result is limited by the fact that the study was a before-after study and lacked a control group. Indeed, there was no significant difference in serum zinc level before and after therapy, which could be due to either insufficient dose of supplementation or the short duration of therapy; however, BMI was also interestingly increased after the zinc administration and there was a slight shift to higher BMI categories. Our results are in agreement with a previous meta-analysis of 33 randomized controlled trials that confirmed the effects of zinc supplementation in improving linear growth and weight gain in children with growth retardation[30]. The effect of zinc supplementation on growth acceleration in CF patients has been shown previously[16]. While zinc has no pharmacologic effect on growth, a growth response to zinc is taken as evidence of a preceding growth-limiting zinc deficiency[31].

The number of hospitalizations was also significantly reduced after zinc administration in this study. This could be due to the preventive effect of zinc on pneumonia, which is a major cause of hospitalization in these patients. Hospitalization is a great source of medical care costs among CF patients. Thus, to facilitate a decrease in the number of hospitalizations and consequently in the cost of medical care, use of supplementary zinc could be considered in the CF management guidelines. However, FEV1 was decreased after zinc administration in our study, in contrast with previous studies[17,26]. As FEV1 could decrease in CF children over time[26], the decrease in FEV1 in our patients could be because of progression of the respiratory disease. Thus, further studies with a control group are needed to compare the FEV1 change with a group that used supplementary zinc.

This study showed that serum zinc measurements are relatively insensitive in CF patients. Supplementary zinc can increase the BMI of CF patients, mostly in those with normal pulmonary function. While supplementary zinc may decrease the number of hospitalizations, other factors can also influence the number of hospitalizations in these patients. However, it should be noted that we did not check the patients' mutations, sputum cultures, or clinical and radiological scores, and therefore, we could not measure these parameters according to the zinc values, which are the weak points of this study. Further studies in different regions and with a control group are needed to confirm the results of this study.

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