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Original Article

Zinc Supplementation Improves Nocturnal Asthma Symptoms

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Abstract:
Background: Treatment of bronchial asthma aims to control the symptoms of bronchoconstriction and disease modification. Zinc influences bradykinin that promotes inflammation and promotes contraction of smooth muscle in the bronchus.
Aim of the work: To test the effect of zinc supplementation on improvement of both clinical symptoms and lung functions in children with bronchial asthma.
Methods: Asthma symptoms, severity and pulmonary function tests were performed to 50 children with bronchial asthma before and after zinc supplementation (1mg/kg/ day) as adjuvant therapy. Serum zinc levels were assessed at initial enrollment for all 50 children.
Results: The studied cohort comprised 28 boys and 22 girls with age range of 6-13 years and mean age +/- SD of 8.88 +/- 2.24 years. Of them 48 %, 30 % and 22% were diagnosed: moderate persistent asthma, mild persistent and severe persistent asthma respectively. Initial serum zinc level was low in 34% of patients (mean 47.2 ±10.8 µg/dl) and 66% of patients had a normal initial serum zinc level (mean 100.6 ± 27.2 µg/dl). After 8 weeks of zinc supplementation there was a significant improvement in decreasing frequency of attacks ($p=0.036$), nocturnal symptoms ($p< 0.001$), clinical control of asthma symptoms ($p< 0.001$) and pulmonary functions showed significant improvement in forced expiratory volume in 1 second (FEV1) ($p<0.001$) and forced vital capacity (FVC) ($p=0.002$) but there was no significant difference in the frequency of daytime symptoms ($p>0.05$), limitation of activities ($p>0.05$) or need for reliever medications ($p>0.05$).
Conclusion: Zinc is an effective adjuvant in controlling nocturnal symptoms and significantly improves pulmonary functions even if the initial serum zinc level was within the normal range.

Level of Evidence of Study: IIB (*1*).
Keywords: bronchial asthma; symptoms; nocturnal cough; zinc sulfate.
Abbreviations: FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity.

Introduction

Bronchial asthma is an atopic disease characterized by chronic airway inflammation and hyper-responsiveness. Severe acute asthma is a medical emergency and sometimes difficult to treat (*2*). Asthma is a major public health problem affecting an estimated 262 million people worldwide and was responsible for 461 thousand deaths in 2019 (*3*). It is the commonest chronic disease among children (*4*). Asthma etiology is multiplex involving host susceptibility, triggering factors and immune response (*5*). Its treatment aims to control the symptoms of bronchoconstriction and disease modification (*6*). Studies suggested that nutritional deficiencies and trace elements levels might be involved in inflammatory processes of asthma (*7*, *8*).

Zinc is a known component of antioxidant enzymes, protects against lipid peroxidation, affects gene expression and has multiple effects on immune response. Zinc deficiency is considered a potential aggravating factor in asthma (*9*, *10*). One-third of the world population is at risk of zinc deficiency (*11*). The inability to store zinc, necessitates its continuous

supplementation in diet. Hence, the effects and spectrum of zinc deficiency are diverse and affected by diet and nutritional status (*10*, *11*).

We hypothesized that zinc supplementation would improve both clinical symptoms and lung functions in cases of persistent bronchial asthma in children. The aim of this study was to evaluate the serum zinc level in a group of Egyptian children with different grades of persistent asthma and to test the effect of zinc supplementation on improvement of both clinical symptoms and lung functions in those children.

Subjects and Methods

This clinical trial was conducted at Specialized Children's Hospital, Faculty of Medicine, Cairo University, Egypt. It commenced April 2016 and ended by December 2016. An informed verbal consent was obtained from parents / surrogates before enrollment. The study design conformed with the requirements of Revised Helsinki Declaration of Bioethics (2013) (*12*). The study was approved by The Scientific Ethics Committee of Pediatrics Department, Faculty of Medicine, Cairo University and Higher Studies Research Committee of Faculty of Medicine.

Participants

Fifty children aged 6- 13 years were enrolled in this study. They were diagnosed with mild, moderate and severe persistent bronchial asthma according to National Asthma Education and Prevention Program, EPR-3, 2007 (*13*) and Children GINA 2018 (*2*). Children with associated diseases or in respiratory failure were not included in this study. Medical history of enrolled children was recorded. Initial and follow up clinical examination of chest and other systems, change in asthma severity or severity of asthma exacerbations according to National Heart, Lung and Blood Institute (NHLBI) (*14*) were also recorded.

Methods

Assessment of Serum Zinc

Serum zinc level was measured by atomic absorption spectrometer in 5 cc blood sample. Serum zinc level was expressed in µg/dl. It was assessed prior to zinc supplementation. The reference normal range of serum Zinc in the current study was 70 - 125 µg/dL (*15*, *16*).

Assessment of Pulmonary Functions

All children were tested using spirometry (Master Screen PFT by JAEGER; Germany). Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and forced expiratory volume in 1 second / forced vital capacity ratio (FEV /FVC ratio) were measured. They were performed before and after zinc supplementation.

Zinc Supplementation

After initial assessment of serum zinc level at baseline, 1mg/kg/day elemental zinc in the form of Zinc sulfate ($ZnSO_4$) was given as syrup with a maximum dose of 12 mg zinc per day up to 8 years and 23 mg zinc per day up to 13 y, it was given as a single daily dose or in divided doses for 8 weeks. Reassessment of asthma control and grading of asthma was done after 8 weeks of zinc supplementation. Serum zinc level was not reassessed at end of trial.

Statistical Analysis

Statistical analysis was performed with the statistical package for social science (IBM SPPS) version 24. Numerical data were tabulated and presented as mean and standard deviation, or medians and ranges. Categorical data were summarized as percentiles. Comparisons between the two groups were calculated using the student T test. Correlation between variables was evaluated using Pearson's correlation coefficient. P-values less than 0.05 were considered as statistically significant.

Results

The studied cohort comprised 28 boys and 22 girls with age range of 6-13 years and mean age ± SD of 8.88 ± 2.24 years. (Table 1). Among the study population 48 %, 30 % and 22% were diagnosed as having moderate persistent asthma, mild persistent and severe persistent asthma respectively. Of the enrolled children 58% were living in urban areas, while 26% in rural areas

and 16% were living in semi-urban areas. At the time of initial enrollment in the study all patients had wheezes and cough, 66% had dyspnea, 4% had cyanosis and 52% had sputum and expectoration. The mean serum zinc level was 76.8 ± 35.1µg/dl for all patients enrolled in this study, and 34% of patients had low initial serum zinc level with mean 47.2 ±10.8 µg/dl and 66% of patients had a normal initial serum zinc level with mean 100.6 ± 27.2µg/dl (Figure1). There was no significant correlation between initial low serum zinc level of patients and severity of asthma (r =-0.078; p=0.601) neither the patient age (r = 0.115; p=0.426), or gender (r = -0.178; p=0.226). The mean serum zinc level was 76.8 µg/dl for all patients enrolled in this study. Normal Serum Zinc Range: 70 - 125 µg/dL. Low mean initial serum zinc level was 47.2 ±10.8 µg/dl and 66% of patients had a normal initial serum zinc level with mean 100.6 ± 27.2 µg/dl. Serum zinc levels was not influenced by gender. (Tables 1 and 2).

Table 1. Initial Serum Zinc Level of Enrolled Patients.

	Gender				
	28 Males		**22 Females**		**P value**
	Mean	**SD**	**Mean**	**SD**	
Initial zinc Level (Normal Range: 70 - 125 µg/dL)	86.4	39.7	69.3	26.3	0.111

SD = standard deviation.

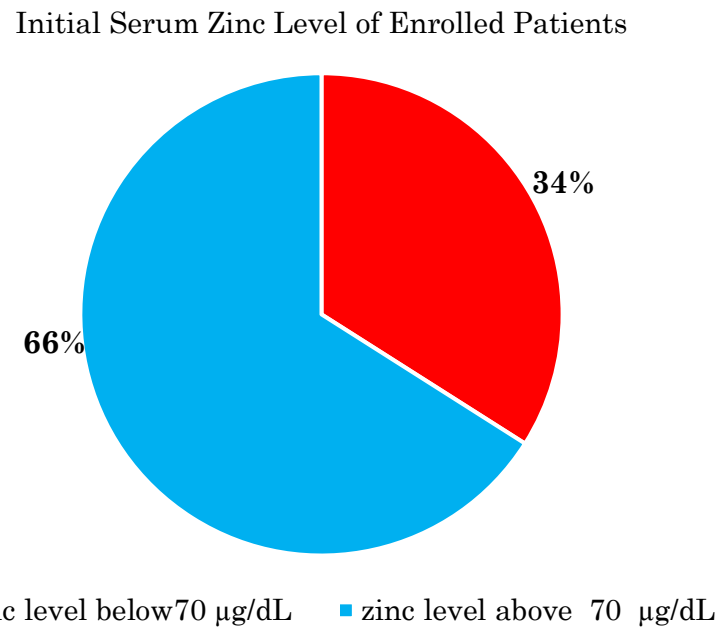

Figure 1. Frequency of those with low and normal levels of serum zinc.

Effect of Zinc Supplementation

In all patients , zinc supplementation resulted in a significant improvement in decreasing frequency of attacks (p=0.036), nocturnal symptoms (p< 0.001) and clinical control of asthma symptoms (p<0.001) but there was no significant difference in the frequency of daytime symptoms (p>0.05), limitation of activities (p>0.05) or need for reliever medications (p>0.05). Also Zinc supplementation caused a significant improvement in all pulmonary functions including FVC, FEV1 and FEV1/FVC ratio. While, in patient group with initial low serum zinc level, there was significant improvement in nocturnal symptoms (p< 0.001) and clinical control

of asthma symptoms (p=0.006) after zinc supplementation compared to pre-zinc supplementation.

Table 2: Relation between severity of asthma, gender and serum zinc level.

		Serum Zinc level				P value
		Low (below70 µg/dL)		Normal (above70 µg/dL)		
		Count	%	Count	%	
Grade of persistent asthma	Mild	4	8	11	22	0.799
	Moderate	9	18	15	30	
	Severe	4	8	7	14	
Gender	Males (29)	11	22	18	36	0.4933
	Females (21)	10	20	11	22	
Total		17	34	33	66	

There was no significant difference in frequency of attacks (p>0.05), daytime symptoms (p>0.05), limitation of activities (p>0.05) or need for reliever (p>0.05). Also, pulmonary functions showed significant improvement in FEV1 (p<0.001) and FVC (P=0.002) (Table 3,4, 5).

Table 3: Clinical control of asthma before and after zinc supplementation

		Before zinc		After zinc		P value
		Count	%	Count	%	
Frequency of attacks/month before and after zinc supplement)	2	2	4	6	12.0	0.036
	3	7	14.0	9	18.0	
	4	7	14.0	16	32.0	
	5	18	36.0	13	26.0	
	6	10	20.0	3	6.0	
	7	3	6.0	3	6.0	
	8	3	6.0	0	0	
daytime symptoms > twice a week	Y	38	76.0	29	58.0	0.056
	N	12	24.0	21	42.0	
Limitations of activities	Y	2	4.0	1	2.0	1
	N	48	96.0	49	98.0	
Nocturnal symptoms/awakenings	Y	32	64.0	6	12.0	< 0.001
	N	18	36.0	44	88.0	
Need for reliever > twice a week	Y	27	54.0	23	46.0	0.424
	N	23	46.0	27	54.0	
Control	Well	10	20.0	19	38.0	< 0.001
	Partly	17	34.0	28	56.0	
	Uncontrolled	23	46.0	3	6.0	

Table 4: Pulmonary functions before and after zinc supplementation

	Mean level ± SD before zinc supplementation	Mean level ± SD after zinc supplementation	P value
Pulmonary functions among studied cohort (50 children)			
FEV1	84.6 ± 10.6	90.48 ± 9.48	< 0.001
FVC	89.72 ± 9.7	94.35 ± 9.12	0.001
FEV1/FVC	93.68 ± 10.98	95.83 ± 8.57	0.043
Pulmonary functions among patient group (17 children) with low initial serum zinc level			
FEV1	82.94 ± 10.47	92.44 ± 10.74	<0.001
FVC	90.24 ± 11.28	99.38 ± 9.61	0.002
FEV1/FVC	92.65 ± 12.03	93 ± 7.54	0.597

FVC=forced vital capacity; FEV1=forced expiratory volume in 1 second.

Table 5: Clinical control in patient group with initial low serum zinc level before and after zinc supplementation

		Before zinc		After zinc		P value
		Count	%	Count	%	
Frequency of attacks/month before and after zinc supplement)	3	1	5.9	4	23.5	0.366
	4	5	29.4	8	47.1	
	5	7	41.2	3	17.6	
	6	2	11.8	1	5.9	
	7	1	5.9	1	5.9	
	8	1	5.9	0	.0	
daytime symptoms>twice a week	Y	15	88.2	11	64.7	0.225
	N	2	11.8	6	35.3	
Limitations of activities	Y	1	5.9	1	5.9	1
	N	16	94.1	16	94.1	
Nocturnal symptoms/awakenings	Y	12	70.6	0	.0	< 0.001
	N	5	29.4	17	100.0	
Need for reliever >twice a week	Y	11	64.7	10	58.8	0.742
	N	6	35.3	7	41.2	
Control	Well	1	5.9	4	23.5	0.006
	Partly	7	41.2	12	70.6	
	Uncontrolled	9	52.9	1	5.9	

Discussion

Zinc deficiency was not a constant finding among our studied cohort of children with bronchial asthma. It affected only a third of our studied cohort, and did not corelate with asthma severity. Zinc supplementation was effective in achieving control of nocturnal symptoms and better sleep. It did not reduce the need for asthma reliever medications or daytime symptoms. Pulmonary functions improved after zinc supplementation irrespective of initial serum zinc level. The response to serum zinc supplementation in asthma is conflicting, yet the nocturnal control of asthma symptoms seems to be a constant finding. A lot of factors seem to control the response to zinc supplementation.

Dose and spacing regimen seem to affect response, where alternate day therapy of 50 mg of elemental zinc seems to offer lesser control of symptoms tests (*17*). Bigger doses of zinc of 50mg/ day were reported to achieve better control (*18*). Yet, improvement of pulmonary function was constant in both regimens. Pulmonary functions improvement might be related to effect of zinc on muscles especially on skeletal muscles, but the effect on muscles is related to myogenesis and muscle regeneration (*19*), hence it would be expected that the effect of zinc would need protracted duration to achieve an effect. Yet, in our study, as well as others the improvement was seen in a month duration. Hence we assume that zinc has another more rapid effect on respiration.

Other factors may be responsible for the inconsistent effect of zinc in asthma. The plasma level of zinc does not reflect the differential distribution of zinc among the different tissues, where zinc is most abundant in bone and muscles and least in heart and brain (*20*, *21*). Hence, the true needed dose might need more of individualization, or titration to achieve effect, rather than a standard regular dose. Again the distribution for zinc among tissues is relevant to its need, which might not be possible to estimate without invasive methods. Hence, it will be mostly for experimental purposes, and does not carry the convenience for patient use.

Again zinc reduces some metalloenzymes (*22*). Metalloenzymes inhibitors are targets for asthma therapy (*23*, *24*). Yet, many factors govern the response of asthma to metalloenzyme inhibitors. Angiotensin-converting enzyme (ACE) is zinc dependent. ACE degrades bradykinin, that promotes inflammation and promotes contraction of smooth muscle in the bronchus(*25*).

Zinc bioavailability is another factor that controls the response to zinc(*26*).

The multifaceted role of zinc on respiration warrants longer duration studies to define the needed duration to achieve control of nocturnal symptoms of asthma and maintained effect of improvement of pulmonary functions. Yet, it should be noted that once serum levels are low, then tissue levels are deficient and the need to replenish the zinc stores would take time. Again the normal zinc serum level does not necessarily mean normal tissue levels of zinc (*26*).

The limitations of our current study, is the small number of enrolled children, lack of control group and short duration of the study.

Conclusions

Zinc is an effective adjuvant in controlling nocturnal symptoms. Its use is associated with significant improvement in pulmonary functions. Zinc potential role in control of day time asthma symptoms remains to be studied.

Author Contributions:

All authors shared in conceptualization, supervising, data curation, data analysis, writing original draft, data interpretation, writing original draft, supervising and revising. All authors reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the study.

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