



Association of serum zinc levels and symptom control of asthma in children and adolescents— a prospective observational study

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Abstract

Dysregulation of zinc (Zn) homeostasis causes a shift in the Th1/Th2 balance towards a Th2 response, which may lead to a heightened inflammatory response. Asthma is associated with an exaggerated Th2 response to antigens. This study attempts to find the association of serum Zn with the status of symptom control of asthma in children and adolescents with bronchial asthma. A total of 67 asthmatic children, diagnosed as per Global Initiative for Asthma (GINA) 2019 guidelines, were included in the study. Symptom control of asthma was assessed by Asthma Control Test (ACT) and Childhood Asthma Control Test (C-ACT) scores. Spirometry was performed on those participants who were able to perform satisfactorily. Serum Zn was analyzed using the photometric method. Participants were divided into two groups: controlled and uncontrolled groups according to ACT/C-ACT score. Mean age of the participants was 10.78 ± 3.67 years. The mean S. Zn ($\mu\text{g/dL}$) was 136.97 ± 48.37 . This study found a higher mean S. Zn value in the controlled asthma group as compared to the uncontrolled group (158.06 vs 129.23 , $p=0.006$). At a cutoff of S. Zn ($\mu\text{g/dL}$) ≥ 126.84 , it predicted controlled asthma with a sensitivity of 89% and a specificity of 55%. No significant difference was found between the mean serum Zn levels in terms of age, sex, severity, and CRP levels.

Conclusion: A significant difference was observed between the mean value of Zn and symptom control of asthma ($p=0.006$) with a weak positive correlation between the two which was statistically significant ($\rho=0.26$, $p=0.031$). However, low levels of zinc were not significantly associated with symptom control of asthma. Thus, we conclude that maintaining an adequate zinc level could help in achieving better control of asthma in pediatric populations.

What is Known:

- Zinc has a role in immunological response in the pathophysiology of immunological disorders such as bronchial asthma.

What is New:

- This study adds a significant association of serum zinc levels with symptom control of asthma in pediatric populations.
- This study also gives a cut-off value of serum zinc level which predicts adequate symptom control of asthma.

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Keywords Asthma control · Asthma Control Test · Serum zinc level

Abbreviations

ACT	Asthma Control Test
CBC	Complete blood count
C-ACT	Childhood Asthma Control Test
CRP	C-reactive protein
EDTA	Ethylenediaminetetraacetic acid
FEV1	Forced expiratory volume in 1st second
GINA	Global Initiative for Asthma
IL	Interleukin
LMICs	Low- and middle-income countries
NCD	Non-communicable diseases
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2

Introduction

Asthma is one of the most common non-communicable diseases (NCDs) affecting both children and adults. It affected around 262 million people in 2019 and caused 461,000 death all over the world [1]. Mortality due to asthma mostly occurs in low- and middle-income countries (LMICs) where underdiagnosis and under-treatment are a challenge [2]. As there is no permanent cure for asthma, the goal of asthma management is directed to achieve optimal control of symptoms, maintain normal activity, minimize the risk of future exacerbations, and minimize the side effects related to treatment [3, 4]. Zinc (Zn) is an important trace element that has a critical role in various physiological processes such as growth and development, maintenance and priming of the immune system, tissue repair, and regeneration. Zn has been shown to have a vital role as an anti-oxidant, microtubule stabilizer, anti-apoptotic agent, growth cofactor, and anti-inflammatory agent in various tissues [5]. Dysregulation of Zn homeostasis causes a shift in the Th1/Th2 balance towards a Th2 response, which may lead to a heightened inflammatory response. A fundamental abnormality in asthma is an exaggerated Th2 response to normally harmless environmental antigens. Th2 cells secrete cytokines that promote inflammation and stimulate B cells to produce IgE and other antibodies. These cytokines include IL-4, which stimulates the production of IgE; IL-5, which activates locally recruited eosinophils; and IL-13, which stimulates mucus secretion from bronchial submucosal glands and also promotes IgE production by B cells [6–8]. As a result, greater demand of Zn by the immune system could be a contributing factor to Zn deficiency in inflammatory conditions like asthma.

Only a few studies in the literature show low levels of Zn in patients with uncontrolled asthma, especially in children. Furthermore, there is a paucity of evidence examining whether alteration in serum levels of zinc adversely affects symptom control in children and adolescents with asthma. This study is proposed to explore this research question.

Materials and method

This was a hospital-based cross-sectional study carried out from January 2020 to June 2021. A total of 67 children and adolescents aged 5–18 years, attending outpatient/inpatient department, diagnosed with bronchial asthma as per GINA 2019 guidelines were included in the study (Table 1). Children with conditions that could affect serum zinc levels such as acute infections; systemic diseases like liver, renal, endocrine, cardiovascular, and immunodeficiency diseases; severe malnutrition; systemic steroids; diuretics; proton-pump inhibitors; and magnesium supplementations were excluded from the study. A pre-structured proforma was used to collect the demographic data, age of onset of the disease, symptomatology, duration of the disease, triggering factors, number of exacerbations, treatment details, and adherence to the treatment. All the patients were subjected to complete physical examination, complete blood count (CBC) with differential white cell counts, C-reactive protein (CRP), serum magnesium levels, and ACT/C-ACT. Under all aseptic precautions, 5 ml of venous blood samples was collected from each patient into 2 vacutainer vials. Two milliliters was poured into an EDTA vial for CBC and the remaining 3 ml into a plain vial for CRP and zinc levels. Zinc deficiency is defined as S. Zn level < 60mcg/dL. The CBC samples were analyzed using Beckman Coulter LH 750 Hematology. CRP and zinc levels were analyzed using Beckman Coulter AU680/AU480, using a photometric method in the biochemistry laboratory. Spirometry standardized as per American Thoracic Society guidelines was also done for those patients who were cooperative and who could do it satisfactorily (Table 2). RMS Helios 401 PC-based spirometer was used for spirometry. Asthma Control Test (ACT) was used to assess the status of symptom control in adolescents aged 12–18 years. Childhood Asthma Control Test (C-ACT) was used for children aged 5 to 11 years. Cases were categorized into the following three groups:

- Children with ACT/C-ACT > 19 and ACT/C-ACT ≤ 19.
- Children with FEV1 > 80% and FEV1 < 80% of the predicted value on spirometry.
- Children with CRP < 6 mg/L and CRP > 6 mg/L.

Table 1 Socio-demographic, asthma severity, and symptoms control of study participants

Parameters	Mean \pm SD median (IQR) min–max frequency (%)
Age (years)	10.78 \pm 3.67 11.00 (8.00–14.00) 5.00–18.00
Sex	
Male	43 (64.2%)
Female	24 (35.8%)
Socio-economic status	
Upper	1 (1.5%)
Upper middle	13 (19.4%)
Lower middle	33 (49.3%)
Upper lower	20 (29.9%)
Age of onset (years)	6.54 \pm 4.03 6.00 (4.00–9.00) 0.50–16.00
Allergic rhinitis	50 (74.6%)
Diet	
Vegetarian	48 (71.6%)
Mixed	19 (28.4%)
Family history (yes)	19 (28.4%)
Severity	
Intermittent	23 (34.3%)
Mild persistent	26 (38.8%)
Moderate persistent	16 (23.9%)
Severe persistent	2 (3.0%)
Asthma control	
Controlled	18 (26.9%)
Uncontrolled	49 (73.1%)
ACT/C-ACT score	17.60 \pm 4.41 17.00 (15.00–22.00) 7.00–27.00

Statistical analysis

SPSS version 23 was used for analysis. Chi-square or Fisher exact test was used for categorical variables. Independent sample *t*-test and appropriate non-parametric tests were used when comparing two groups for continuously and non-normally distributed data, respectively. Linear correlation

between two continuous variables was done using Pearson's correlation (normally distributed data) and Spearman's correlation (for non-normally distributed data). For all comparisons, 5% probability (*p*-value less than 0.05) was considered significant. The Institute Ethics Committee approved the study. Informed consent was obtained from parents/legally authorized representatives.

Table 2 S. Zinc, CRP level, and FEV1 (spirometry) of study participants

Investigations	Mean \pm SD median (IQR) min–max frequency (%)
FEV1 (%)	79.12 \pm 9.49 78.00 (72.50–86.00) 46.00–98.00
FEV1	
< 80%	22 (51.2%)
> 80%	21 (48.8%)
CRP (mg/L)	5.61 \pm 5.56 3.20 (2.00–8.10) 0.08–23.00
CRP	
< 6 mg/L	45 (67.2%)
> 6 mg/L	22 (32.8%)
S. Zinc (μg/dL)	136.97 \pm 48.37 130.36 (106.07–162.74) 50.84–293.00
S. Zinc	
< 60 μ g/dL	3 (4.5%)
\geq 60 μ g/dL	64 (95.5%)

Results

We screened a total of 72 children with asthma. Of 72 children, five were excluded as two had the existing nephrotic syndrome, two had acute febrile illnesses, and one was on systemic corticosteroids. Finally, we evaluated 67 asthmatic children, aged 5–18 years with males comprising 64.2% and females being 35.8% with male to female ratio: 1.8:1. The mean age of the participants was 10.78 \pm 3.67 years. Most of the participants belonged to the age group 5–12 years (64.2%) (*n* = 43). Most of the participants belonged to the lower middle class (49.3%) which was followed by the upper lower class (29.9%), upper-middle-class (19.4%), and upper class (1.5%). The mean age of onset of symptoms was 6.54 \pm 4.03 years. Nineteen children (28.4%) had a history of asthma in family members. Most of the participants were vegetarian by diet (71.6%). Most of the patients were with

intermittent (34.3%) and mild persistent severity (38.8%) of asthma. Eighteen (26.9%) of the participants belonged to the controlled group. The majority of the study subjects belonged to the uncontrolled group, comprising 73.1% ($n=49$). Twenty-two children (51.2%) had $FEV1\% < 80\%$ and 21 (48.8%) had $FEV1\% > 80\%$. The mean S. Zinc ($\mu\text{g/dL}$) was 136.97 ± 48.37 . Three (4.5%) of the participants had S. Zinc: $< 60 \mu\text{g/dL}$. Sixty-four (95.5%) of the participants had S. Zinc: $\geq 60 \mu\text{g/dL}$. The mean age (years) of the patients in the uncontrolled group was significantly higher than the patients in the controlled group (11.37 ± 3.76 vs 9.19 ± 2.97 , p -value 0.034). There was no significant difference between asthma control in regards to sex, socioeconomic status, family history, and BMI. Significant difference was found between level of asthma control and CRP levels with patients in controlled asthma having lower CRP levels $< 6 \text{ mg/L}$ [16 (88.9%) vs 29 (59.2%), $p=0.022$]. No significant difference was found between the mean of S. Zinc levels in terms of age, sex, severity, and CRP levels. However, a statistically significant difference was found between the mean of serum zinc levels and level of symptom control of asthma with patients in the controlled group having higher zinc value as compared to the uncontrolled group [158.06 (41.71) vs 129.23 (48.71), $p=0.006$]. A weak positive correlation was observed between ACT/C-ACT score and S. Zinc (mg/dL) and this was statistically significant ($\rho=0.26$, $p=0.031$). No significant difference was observed between hypo-zincemia (S. Zn $< 60 \mu\text{g/dL}$) in terms of severity, asthma control, and CRP levels. The area under the ROC curve (AUROC) (Fig. 1) for S. Zinc ($\mu\text{g/dL}$) predicting controlled asthma vs uncontrolled asthma was 0.721 (95% CI: 0.594–0.848), thus demonstrating fair diagnostic performance. It was statistically significant ($p=0.006$). At a cut-off of S. Zinc ($\mu\text{g/dL}$) ≥ 126.84 , it predicted controlled asthma with a sensitivity of 89% and a specificity of 55% (Table 3).

Discussion

In our study, asthma prevalence was higher in boys than girls. A possible explanation for this could be that the growth of large airways lags behind the growth of lung parenchyma leading to narrower airways in boys than girls and also there is an increased immunological response in boys than girls [9]. The mean age in our study was found to be 10.78 ± 3.67 years. In a similar cross-sectional study done by AbdulWahab et al. [10], the mean age of asthmatic children was 10.92 ± 1.81 years. The present study also showed a high proportion of allergic rhinitis (74.6%) in asthmatic patients. This supports the finding that over 80% of asthmatics have allergic rhinitis [11].

Our study found a statistically significant difference between two groups. i.e., controlled and uncontrolled groups

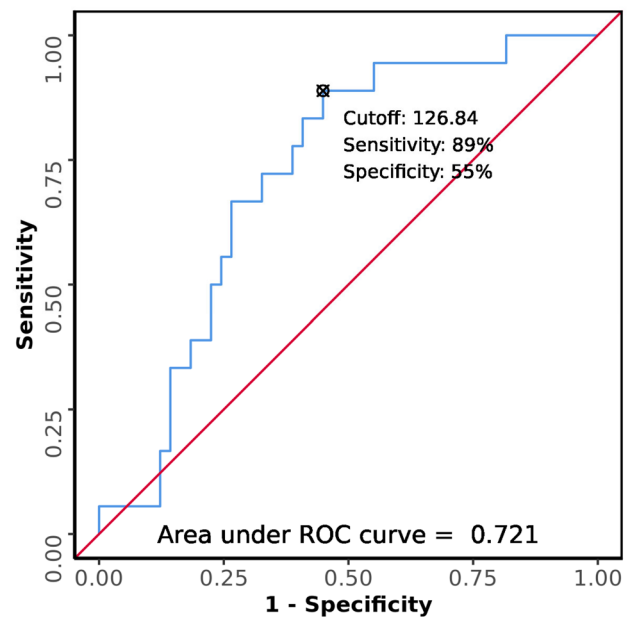


Fig. 1 ROC curve analysis showing diagnostic performance of S. Zinc ($\mu\text{g/dL}$) in predicting asthma control: controlled vs uncontrolled ($n=67$). The area under the ROC curve (AUROC) for S. Zinc ($\mu\text{g/dL}$) predicting the level of asthma control (controlled vs uncontrolled) was 0.721 (95% CI: 0.594–0.848), thus demonstrating fair diagnostic performance. It was statistically significant ($p=0.006$). A cut-off of S. Zinc ($\mu\text{g/dL}$) ≥ 126.84 predicted asthma control with a sensitivity of 89% and a specificity of 55%. The odds ratio (95% CI) for controlled asthma, when S. Zinc ($\mu\text{g/dL}$) is ≥ 126.84 , was 6.14 (1.57–23.94). The relative risk (95% CI) of controlled asthma, when S. Zinc ($\mu\text{g/dL}$) is ≥ 126.84 , was 4.05 (1.44–12.37)

in terms of distribution of CRP ($p=0.022$). Larger proportions of participants in the uncontrolled group had CRP levels $> 6 \text{ mg/L}$ as compared to the controlled group (20, 40.8% vs 2, 11.1%). A similar finding was noted in a study done by Kilic et al. [12]. This finding strengthened our study as more uncontrolled cases based on ACT had significantly higher CRP than those in controlled cases as CRP is considered one of the sensitive markers of inflammation.

The mean S. Zinc ($\mu\text{g/dL}$) was 136.97 ± 48.37 and 3 (4.5%) participants had S. Zinc: $< 60 \mu\text{g/dL}$. A cross-sectional study conducted by Ribeiro-Silva et al. [13] assessed the influence of serum zinc status on the prevalence of wheezing among 6–12 years children. They found mean serum zinc level was $114 \pm 22.9 \text{ mcg/dL}$ with a prevalence of serum zinc deficiency defined as S. Zn level $< 70 \text{ mcg/dL}$ of 1.5% (95% CI 0.8–2.4). The study also showed a positive and significant association between low serum zinc levels and wheezing in children.

The current study reported a statistically significant difference between the median of zinc (mg/dL) and the level of asthma control (159.24 vs 120.4, $p=0.006$) and a weak positive correlation between ACT/C-ACT score and zinc levels which was statistically significant ($\rho=0.26$,

Table 3 Association between level of asthma control and various parameters

Parameters	Asthma control		p-value
	Controlled (n = 18)	Uncontrolled (n = 49)	
Age (years)***	9.19 ± 2.97	11.37 ± 3.76	0.034 ^a
Sex			0.372 ^b
Male	10 (55.6%)	33 (67.3%)	
Female	8 (44.4%)	16 (32.7%)	
Socio-economic status			0.618 ^c
Upper	0 (0.0%)	1 (2.0%)	
Upper middle	2 (11.1%)	11 (22.4%)	
Lower middle	11 (61.1%)	22 (44.9%)	
Upper lower	5 (27.8%)	15 (30.6%)	
Severity***			< 0.001 ^c
Intermittent	15 (83.3%)	8 (16.3%)	
Mild persistent	3 (16.7%)	23 (46.9%)	
Moderate persistent	0 (0.0%)	16 (32.7%)	
Severe persistent	0 (0.0%)	2 (4.1%)	
ACT/C-ACT score***	23.00 ± 2.03	15.61 ± 3.22	< 0.001 ^d
FEV1 (%)***	88.33 ± 3.97	76.68 ± 9.03	< 0.001 ^a
FEV1***			< 0.001 ^c
< 80%	0 (0.0%)	22 (64.7%)	
> 80%	9 (100.0%)	12 (35.3%)	
CRP (mg/L)	3.45 ± 2.69	6.41 ± 6.13	0.092 ^a
CRP***			0.022 ^b
< 6 mg/L	16 (88.9%)	29 (59.2%)	
> 6 mg/L	2 (11.1%)	20 (40.8%)	
S. Zinc (µg/dL)***	158.06 ± 41.71	129.23 ± 48.71	0.006 ^a
S. Zinc			0.558 ^c
< 60 µg/dL	0 (0.0%)	3 (6.1%)	
≥ 60 µg/dL	18 (100.0%)	46 (93.9%)	

***Significant at $p < 0.05$ ^aWilcoxon-Mann-Whitney U test^bchi-squared test^cFisher's exact test^d t -test

$p = 0.031$). In a similar cross-sectional study done by AbdulWahab et al. [10], they found no statistically significant association between the degree of asthma control and zinc levels (mmol/L) among asthmatic patients ($p = 0.053$). Whereas, in a cross-sectional case-control study done by Andino et al. [14] assessing serum levels of vitamin A (mg/dL) and zinc (mg/L) among moderate to severe persistent asthmatic children aged 8–18 years, a significantly lower median serum zinc and vitamin A values were observed among asthma patients than those among control subjects ($p = 0.0110$ and $p = 0.0303$ respectively).

In the study by Wahab et al., no significant correlation was found between the Zn level and FEV1% ($p = 0.405$) [10]. Various previous studies have shown a significant difference between mean zinc levels between asthmatic patients

and healthy controls [15–19]. The plausible reason for such finding suggests the heterogeneity of these studies, small sample sizes, and various cut-off levels of zinc in the respective studies. Most of the studies compare the levels of zinc between asthmatic patients and healthy control groups. On the other hand, our study was one such study in which we evaluated the levels of serum zinc in asthmatic children between controlled asthma and uncontrolled asthma. Hence, our finding suggests the role of zinc in the level of control of asthma.

The index study has also outlined the diagnostic performance of both serum zinc in predicting control of asthma. We have found a cut-off value of S. Zinc ($\mu\text{g/dL}$) ≥ 126.84 for predicting asthma control with a sensitivity of 89%, a specificity of 55%, and a high negative predictive value

(93.1%, 95% C.I. 77–99). The diagnostic performance of the cut-off value of S. Zinc was statistically significant ($p = 0.006$). We observed that the cut-off value of zinc was on the higher limit of normal values of zinc, and this could suggest that an adequate amount of serum zinc level could help in better control of asthma. However, our study being a small observational study, a robust clinical trial is needed for it to be put into clinical practice.

Our study is one of the few studies in pediatric asthma investigating the role of serum zinc in the status of symptom control of asthma. Participants included in the study conformed to GINA 2019 guidelines for diagnosis. Those asthmatic children and adolescents with acute infections; systemic diseases like liver, renal, endocrine, cardiovascular, and immunodeficiency diseases; severe malnutrition; taking systemic steroids; diuretics; proton-pump inhibitors; and zinc supplementations were excluded in the study that could affect the serum levels of zinc.

Our study has limitations of being small sample size as the SARS-COV-2 pandemic affected significantly during the study period. The measurement of serum levels of zinc could be another limitation that may not be actual representations of total body stores. Measuring Zn levels in tissues such as RBCs, WBCs, muscle cells, nails, hairs, and urine may have given their true effect on asthma control, in addition to serum levels [20, 21].

Conclusion

We have found a significant difference between the mean value of zinc and symptom control of asthma with a weak positive correlation between the two which was statistically significant. However, low levels of zinc were not significantly associated with symptom control of asthma. Thus, we conclude that maintaining an adequate zinc level could help in achieving better control of asthma in pediatric populations. However, the underpower sample size could have limited our study result; hence, it is premature to say whether zinc supplementation has a role in the control of asthma; thus, further studies are still warranted.

Authors' contributions Prof Nowneet Kumar Bhat, Dr. Rajkumar Sananganba, Dr. Vinod Kumar, and Dr. Manish Kumar conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript. Prof Swathi Chacham and Dr. Prashant Kumar Verma helped with data collection and reviewed the manuscript. Anissa Atif Mirza helped in performing the biochemical test and reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data availability Yes, with corresponding author.

Code availability Not applicable.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Ethics Committee of AIIMS, Rishikesh, India.

Consent to participate Informed, written consent was obtained from the parents of all individual participants included in the study.

Consent to publish Obtained.

Competing interests The authors declare no competing interests.

References

- Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M et al (2020) Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 396(10258):1204–1222
- Asthma. [cited 2021 Oct 31]. Available from: <https://www.who.int/news-room/fact-sheets/detail/asthma>
- Rowe BH, Camargo CAJ (2008) The role of magnesium sulfate in the acute and chronic management of asthma. *Curr Opin Pulm Med* 14(1):70–76
- Gourgoulis KI, Chatziparasis G, Chatziefthimiou A, Molyvdas PA (2001) Magnesium as a relaxing factor of airway smooth muscles. *J Aerosol Med Off J Int Soc Aerosols Med* 14(3):301–307
- Truong-Tran AQ, Carter J, Ruffin R, Zalewski PD (2001) New insights into the role of zinc in the respiratory epithelium. *Immunol Cell Biol* 79(2):170–177
- Orihara K, Dil N, Anaparti V, Moqbel R (2010) What's new in asthma pathophysiology and immunopathology? *Expert Rev Respir Med* 4(5):605–629
- Mims JW (2015) Asthma: definitions and pathophysiology. *Int Forum Allergy Rhinol* 5(Suppl 1):S2–6
- Murdoch JR, Lloyd CM (2010) Chronic inflammation and asthma. *Mutat Res* 690(1–2):24–39
- Shah R, Newcomb DC (2018) Sex bias in asthma prevalence and pathogenesis. *Front Immunol* 18(9):2997
- AbdulWahab A, Zeidan A, Avades T, Chandra P, Soliman A (2018) Serum zinc level in asthmatic and non-asthmatic school children. *Child Basel Switz* 5(3):E42
- Egan M, Bunyavanich S (2015) Allergic rhinitis: the “ghost diagnosis” in patients with asthma. *Asthma Res Pract* 1:8
- Kilic H, Karalezli A, Hasanoglu HC, Erel O, Ates C (2012) The relationship between hs-CRP and asthma control test in asthmatic patients. *Allergol Immunopathol (Madr)* 40(6):362–367
- de Cássia R-S, Fiaccone RL, Barreto ML, da Silva LA, Santos LFP, Alcantara-Neves NM (2014) The prevalence of wheezing and its association with serum zinc concentration in children and adolescents in Brazil. *J Trace Elem Med Biol Organ Soc Miner Trace Elem GMS* 28(3):293–297
- Andino D, Moy J, Gaynes BI (2019) Serum vitamin A, zinc, and visual function in children with moderate to severe persistent asthma. *J Asthma Off J Assoc Care Asthma* 56(11):1198–1203
- Ariaee N, Farid R, Shabestari F, Shabestari M, Jabbari AF (2016) Trace elements status in sera of patients with allergic asthma. *Rep Biochem Mol Biol* 5(1):20–25
- El-Kholy MS, Gas Allah MA, El-Shimi S, El-Baz F, El-Tayeb H, Abdel-Hamid MS (1990) Zinc and copper status in children with

- bronchial asthma and atopic dermatitis. *J Egypt Public Health Assoc* 65(5–6):657–68
17. Khanbabaee G, Omidian A, Imanzadeh F, Adibeshgh F, Ashayeripanah M, Rezaei N (2014) Serum level of zinc in asthmatic patients: a case-control study. *Allergol Immunopathol (Madr)* 42(1):19–21
 18. Uysalol M, Uysalol EP, Yilmaz Y, Parlakgul G, Ozden TA, Ertem HV et al (2014) Serum level of vitamin D and trace elements in children with recurrent wheezing: a cross-sectional study. *BMC Pediatr* 16(14):270
 19. Vural H, Uzun K, Uz E, Koçyigit A, Çigli A, Akyol Ö (2000) Concentrations of copper, zinc, and various elements in serum of patients with bronchial asthma. *J Trace Elem Med Biol* 14(2):88–91
 20. Arik Yilmaz E, Ozmen S, Bostanci I, Misirlioglu ED, Ertan U (2011) Erythrocyte zinc levels in children with bronchial asthma. *Pediatr Pulmonol* 46(12):1189–1193
 21. Ghaffari J, Alizadeh-Navaei R, Dabaghzadeh A, Ghaffari N (2021) Serum zinc level and children's asthma: a systematic and meta-analysis review article. *Casp J Intern Med* 12(3):236–242

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