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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

ÇOCUKLUK ÇAĞI ASTIMININ KONTROL VE ŞİDDET DÜZEYİ İLE SERUM ÇİNKO DÜZEYLERİ ARASINDAKİ İLİŞKİ

RELATIONSHIP AMONG SERUM ZINC LEVELS AND SEVERITY AS WELL AS CONTROL OF CHILDHOOD ASTHMA

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ÖZ

AMAÇ: Çocukluk çağı astımı multifaktöriyel bir hastalıktır. Patogenezinde anti-inflamatuvar ve anti-oksidan ajanların önemli rol oynadığı bilinir. Bununla birlikte anti oksidan çinko gibi eser elementlerin rolü ile ilgili farklı görüşler mevcuttur. Bizim çalışmamızın amacı astım kontrol ve şiddeti ile serum çinko düzyleri arasındaki ilişkiyi belirlemekti.

GEREÇ VE YÖNTEM: Çalışmaya Temmuz 2014 ile Nisan 2015 tarihleri arasında 3-17 yaş arası astım tanısı almış 56 hasta ve 26 sağlıklı çocuk alındı. Astım kontrol düzeyleri GINA 2014 kriterlerine göre belirlendi. Serum çinko düzeyleri atomic absorbsiyon spektroskopi metodu ile çalışıldı. Yapılabilen hastalara solunum fonksiyon testleri uygulandı.

BULGULAR: Astım ve kontrol grubu serum çinko düzeyleri arasında anlamlı fark bulunmadı. Serum çinko düzeyleri tam kontrollü astım grubuna göre kısmi kontrollü astım grubunda anlamlı şekilde yüksek bulundu (p=0.023). Astım kontrol düzeyi ile serum çinko düzeyleri arasında anlamlı negative korelasyon izlendi (r: -0.437, p=0.001). FVC %80 altında olan grupta serum çinko düzeyleri anlamlı şekilde yüksek bulundu (p=0.001). Astım şiddet düzeyine göre serum çinko düzeyleri arasında fark bulunmadı (p=0.228). Astım şiddeti ile serum çinko düzeyleri arasında anlamlı korelasyon saptanmadı (r=0.168, p=0.217).

SONUÇ: Serum çinko düzeyleri çocuklarda astım kontrolü ile ilişkili idi. Serum çinko düzeyleri astım kontrol düzeylerini belirlemede diğer parametrelere destekleyici olarak düşünülebilir.

ANAHTAR KELİMELER: Astım, çocukluk çağı, kontrol, şiddet, çinko

ABSTRACT

OBJECTIVE: Childhood asthma is a multifactorial disease. It is known that anti-inflammatory and antioxidant agents play important roles in the pathogenesis of asthma. However, there are conflicting reports about the roles of antioxidant trace elements such as zinc in asthma. The aim of our study was to investigate the relationship between the serum zinc levels and the severity and control of asthma.

MATERIAL AND METHODS: This study enrolled 56 pediatric patients diagnosed with asthma between the ages of 3 to 17 between July 2014 and April 2015, and 26 healthy children. Control levels of asthma were determined based on the Global Initiative for Asthma Guidelines 2014 criteria. Serum zinc levels were studied using the atomic absorption spectroscopy method. Pulmonary function tests were performed on all patients who complied with the spirometry device.

RESULTS: Serum zinc levels were not statistically significant different between the asthma and control groups but significantly higher in the partially controlled asthmatic group compared with the full control asthmatic group (p=0.023). There was a statistically significant negative correlation between the control level of asthma and zinc levels (r: -0.437, p = 0.001). The zinc level in the group with FVC below 80% was significantly higher (p = 0.001). There was no significant difference in zinc levels according to asthma severity (p = 0.228). There was no significant correlation between asthma severity and serum zinc level (r = 0.168, p = 0.217).

CONCLUSIONS: Serum zinc levels were associated with the level of control of astma in children. Serum zinc levels might be considered as a useful biomarker that supports other parameters to determine the level of asthma control in children.

KEYWORDS: Asthma, childhood, control, severity, zinc

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INTRODUCTION

Asthma is a chronic disease with a high morbidity rate among children due to emergency department visits, hospitalization and absence from school. In the last decades, an increase in the prevalence of the disease has been observed. This could be due to environmental, economic and nutritional factors beyond genetic susceptibilities (1,2,3). Asthma principally has a course of chronic inflammation in the airways and usually with bronchoconstriction induced by IgE-mediated type I hypersensitivity. The fact that asthma has high morbidity rates despite effective medication, therefore it necessitates innovative approaches and use of new biomarkers in the diagnosis/treatment of asthma. More recent studies also showed that bronchoconstriction is triggered by proteolytic and oxidative damage in the airway epithelium in addition to airway inflammation (2,4). The airway epithelium may be affected by oxidative damage caused by inflammatory cells and oxidant agents in the air (5,6). Zinc is an essential dietary factor which has anti-inflammatory and anti-oxidant properties, and it is found in the contents of numerous cells of human body and structures of various enzymes (e.g. glutathione peroxidase and superoxide dismutase) in the respiratory tract (7,8). Moreover, zinc is considered to take part in the humoral and cellular immune response and it may play a role in the pathogenesis of asthma because of its anti-apoptotic and anti-inflammatory properties (2,9,10). Therefore it is assumed that the severity of asthma and deterioration in control level of asthma increase in the case of zinc deficiency (2,7,11).

The purpose of our study was to determine zinc levels in children diagnosed with asthma using reliable methods, and to investigate the relationship among the serum zinc levels and the severity with control of asthma.

MATERIALS AND METHODS

Patients and study design

The study enrolled 56 pediatric patients diagnosed with asthma between the ages of 3 to 17 who visited the Pediatric Allergy Polyclinic of the Research and Training Hospital of Sakarya University between July 2014 and April 2015 due to attacks or for routine control, as well as 26 healthy children of similar age and sex distribution. In this study, our exclusion criteria are as following: Patients who had malnutrition, who used medication regularly besides the asthma treatment, who had received zinc treatment in the previous three months, who had another chronic, metabolic disease or malignity, who were diagnosed with immunodeficiency, who had hemorrhagic diathesis, who were admitted with fever, who were using systemic corticosteroids, who did not volunteer for the study and patients with signs of upper respiratory tract infection were barred. Firstly, socio-demographic data and nutritional statuses of the patients were evaluated. Using the obtained blood samples; serum zinc and albumin levels which affect serum zinc levels, white blood cell (WBC) and high sensitive-C reactive protein (hs-CRP) tests as the acute phase reactant were studied. Pulmonary function test was performed.

Ethical approval

The approval for the study was obtained from the Sakarya University ethics committee (Ethics Committee No: 16214662/050.01.04/114).

Clinical and Laboratory Assessment of the Participants

Pulmonary function test was performed with spirometry (MIR Spirolab 3, Italy) on patients over the age of five who were able to cooperate. The Global Initiative for Asthma (GINA) 2014 guidelines were used in asthma diagnosis and classification. Patients were classified based on the GINA criteria as uncontrolled, partly controlled and controlled. Severity of asthma was determined using clinical signs and changes in spirometry values including forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratios, and patients were categorized under five persistence asthma groups as mild, mild-moderate, moderate, moderate-severe and severe persistent.

Venous blood samples for determination of all parameters were collected from subjects in the morning, before food intake. All tubes for Zn

measurement used for blood collection and serum storage were free of trace microelements. The samples were centrifuged and serum was stored at -20°C. The determination of serum Zn levels was performed using a flame atomic absorption spectrometer (Varian AA240). The calibration graphs were constructed using normal aqueous standards (NIST-USA). White blood cell was determined with automated CBC analyzer (Celldyn 3400, Abbott diagnostics, USA) within one hour. Serum albumin level was determined with full-automated analyser (AU 5800, Beckman Coulter, Tokyo, Japan). Serum hs-CRP concentration was determined using the Siemens CardioPhase hs-CRP (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) particle-enhanced immunonephelometric assay on the BN II analyser (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany).

Statistical Analyses

Descriptive statistics were used to examine the general features of the participants. The Shapiro-Wilk test was used to assess the distribution of numerical variables. Those variables with normal distributions are presented as means ± standard deviations. Categorical variables are indicated as number (n) and percentage (%). Student's t-test and ANOVA were used to compare groups. Groups defined by categorical variables were compared using $\chi 2$ tests. For establishing a relationship between numerical variables linear correlation coefficient was calculated. The SPSS software (ver. 20 for Windows; IBM SPSS, Inc., Chicago, IL, USA) was used for statistical analyses.

RESULTS

Demographic data, serum zinc levels, WBC, hs-CRP and albumin levels for asthma and control group are shown in **Table 1**. There were no statistically significant differences in all parameters between the groups. Normal serum zinc level was varying from 75 to 100 µg/dl, according to our laboratory reference value.

It was observed that the differences among controlled (88.66±1.52 µg/dL), partly controlled (89.45±3.93 µg/dL) and uncontrolled (92.61±2.59 µg/dL) groups based on the control levels of asthma were statistically significant (p=0.023, **Figure 1**). However, it was also observed that serum zinc levels increased as asthma control levels decreased, and there was a weak negative correlation between asthma control levels and zinc levels (rs= -0.437, p=0.001, **Figure 2**).

Tablo 1: Demographic characteristics and laboratory data of the asthma and control groups.

Parameters	Asthma Group (n=56)	Control Group (n=26)	*p value*
Gender, F/M	25/31	12/14	0.898
Age, year	8.46±3.26	7.77± 3.08	0.365
Zinc, µg/dL	90.14±3.80	89.26±3.45	0.322
Albumin, g/L	4.48±0.24	4.46±0.22	0.702
WBC, /mm^3	7832.95±2535.32	8193.75±2670.63	0.072
hs-CRP, mg/L	5.61±12.18	5.4341 ±11.08	0.454

hs-CRP: High sensitive C-reactive protein; **F/M**: Female/male; **WBC**: White blood cell.

Figure 1: Changes in serum zinc levels according to asthma control levels

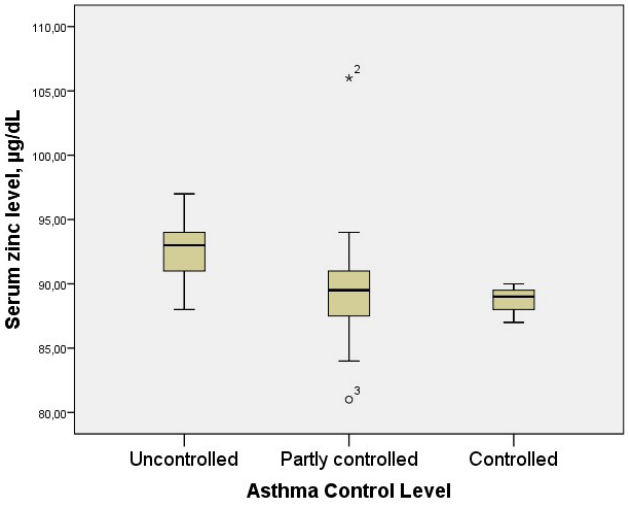
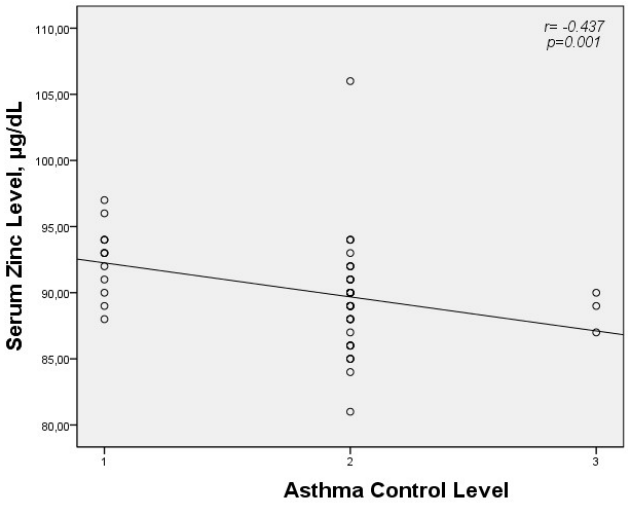
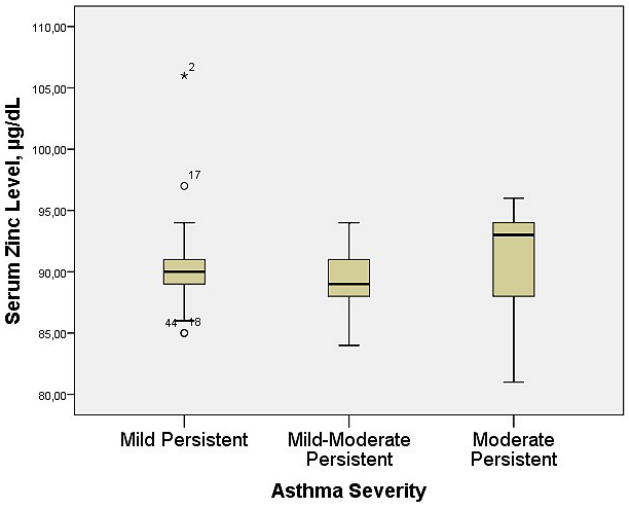


Figure 2: Scatter plot figures for Spearman correlation of asthma control levels and serum zinc levels:



Our study does not include severe persistent patients, as they were also very rarely found in our patient group in the clinic. Serum zinc levels were 90.05±3.80 µg/dL, 89.22±3.38 µg/dL, and 91.00±4.16 µg/dL in mild persistent, mild-moderate persistent, and moderate persistent asthma groups. According to the results of the analysis based on the severity of asthma, no statistically significant differences were observed among groups in terms of serum zinc levels (p=0.228, **Figure 3**). It was demonstrated that there was also no significant correlation between the severity of asthma and zinc levels (r=0.168, p=0.217).

Figure 3: Changes in serum zinc levels according to asthma severity



Among the 37 patients who were subjected to respiratory function tests, serum zinc levels were found no significant difference between FEV1 values below 80% and FEV1 values of 80% or above groups (90.41±4.50 µg/dL, 90.68±3.98 µg/dL, p=0.858). Serum zinc levels were found significantly higher in the group with FVC value below 80% than those with FVC value 80% or above (92.93±4.66 µg/dL, 88.80±2.48 µg/dL, p=0.001). Changes in serum zinc levels according to FEV1 and FVC values were shown in **Figure 4**. Serum zinc levels were significantly higher in patients with FEV1 or FVC below 80% than patients with FEV1 and FVC value of 80% or above [91.87±3.20 µg/dL, 89.61±4.49 µg/dL, p=0.012, (**Figure 5**)]. Moreover, any significant correlation could not be found between serum zinc levels and FEV1 (r=-0.057, p=0.739) and FVC (r=-0.177, p=0.294) values.

Figure 4: Changes in serum zinc levels according to FEV1 and FVC values

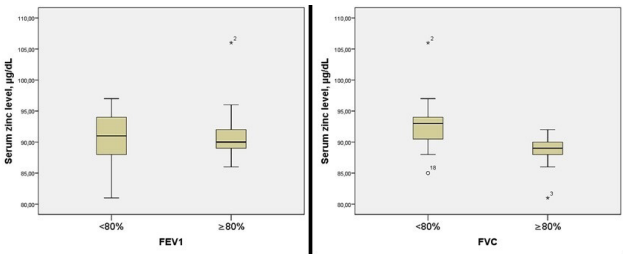
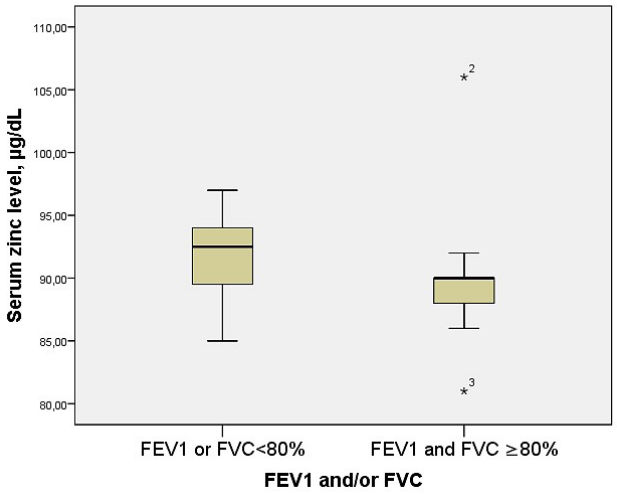


Figure 5: Changes in serum zinc levels according to FEV1 and/or FVC values



DISCUSSION

In our study, serum zinc levels of pediatric asthma patients were found within the normal range and there was no difference found in comparison with serum zinc levels of the healthy control group. While no relationship was observed between persistent asthma and zinc levels, it was also observed that serum zinc levels increased as asthma control levels decreased. In relation to the analysis based on the results of the respiratory function tests in our study, serum zinc levels were found significantly higher in the group with FVC values below 80%.

Bronchial asthma is a disease that has a course with recurrent wheezing induced by chronic inflammation in the airways and bronchoconstriction. Besides inflammation in the airways, bronchoconstriction may also be triggered by various types of proteolytic and oxidative damage. Therefore, it is argued that anti-inflammatory and anti-oxidant agents will prevent the triggering of bronchoconstriction which constitutes the fundamental mechanism in asthma

(4,6,9,12). It has been reported that zinc, which has anti-oxidant, anti-apoptotic, anti-inflammatory and anti-allergic properties, is important in dermatologic and respiratory diseases, while zinc deficiency plays an important role in the pathogenesis and severity of dermatologic and respiratory diseases (2,8,11). Because of its signi-ficant protective role in the airway epithelium, it is suggested that zinc deficiency may lead to an increase in epithelial damage and inflam-mation in airways (13). All of these factors can cause airway inflammation but the certain roles of zinc levels are not clear. In the study by Sağ-dıç et al., there were no differences observed between the control group and the group of patients with asthma and allergic rhinitis in zinc levels (14). Di Toro et al.'s reported that serum zinc levels in children of age 2-14 with asthma and atopic dermatitis did not show differences in comparison to the control group (15). The study by Koçyiğit et al. did not find any differences compared to the control group in serum zinc levels of pediatric asthma patients (16). In the study by Razi et al., hair zinc levels of pe-diatric patients with asthma were not found to be different than the control group (17). The re-sults of our study support the results of studies reporting normal serum zinc levels in pediatric asthmatic patients. The fact that zinc levels of none of our pediatric asthma patient was found to be below normal levels (84-97µg/dl), sugges-ting that daily zinc intakes of the patients were sufficient. However, there has not been any re-ported information on the degree of which se-rum zinc levels represent the enough zinc levels in the study by Lyte et al., in 107 patients of age 10-18 whose asthma control levels described using the GINA criteria, zinc levels of partly controlled and uncontrolled patients were found significantly lower than those of controlled patients (18). While there are similar studies in the literature, there are also studies reporting no relationship between zinc levels and asthma control. In the study by Yılmaz et al. on 67 pediatric asthma patients and 45 healthy children, no difference was found between erythrocyte zinc levels. The same study also reported that there was no relationship found between erythrocyte zinc levels and asthma control (8). In the study by Khanbabaee et al. on 100 children with asthma, no relationship was reported between asthma control and serum zinc levels (19). In our study, based on the results of the analysis conducted regarding asthma control, there was significant difference detected among serum zinc levels of the groups, while levels were found in the normal range for all groups. In addition, negative correlation was observed between the asthma control level and serum zinc levels. In our study, changes in serum zinc levels, even within normal limits, were found to be associated with asthma control. Increased zinc levels with decreased asthma control levels were thought to be related with increased antioxidant capacity against oxidative stress in poorly controlled asthma.

In the randomized placebo-controlled study by Ghaffari et al. on 284 pediatric asthma patients, it was reported that when zinc levels significantly increased, improvements were seen in clinical symptoms such as coughing, wheezing and respiratory distress, and clear recovery of the FVC and FEV1 ratios in the group of patients given 50mg/day of zinc for 8 weeks (20). As opposed to some studies (7), our results raise the question that serum zinc levels might not have a significant effect on bronchoconstriction which leads these patients to develop frequent attacks. There was significantly high serum zinc levels in the group with FVC values of below 80%, although the serum zinc levels of both groups were within the normal range.

Different results have been reported on the relationship between serum zinc levels and the severity of asthma. Studies especially in patients with infantile wheezing reporting increases in attack severity and frequency in lower serum zinc levels are more prominent (17,21,22). The study by Khanbabaee et al. found serum zinc deficiency in 90% of pediatric patients with severe persistent asthma. Consistently, serum zinc levels in pediatric patients with severe persistent asthma were found to be significantly lower than those in patients with mild to moderate persistent asthma (29). In contrast, in a study by Picado et al. on 118 asthma patients and a control group of 121 healthy people, it was determined that there was no significant

difference between serum zinc levels of asthma patients and people in the control group, while it was reported that there was no relationship found between the severity of asthma and serum zinc levels (23). In the study by Iurina et al., it was reported that an increase in zinc levels occurred in parallel with the increase in the severity of the disease (24). In our study, according to the results of the analysis based on the severity of asthma, no statistically significant differences were observed among groups in terms of serum zinc levels. No significant correlation was observed among the severity of asthma and serum zinc levels.

The major limitation of this case-control study was the relatively small number of participants.

In conclusion, our results suggested that there was a relation between serum zinc level and control level of asthma but not with severity. The increase in serum zinc levels can reflect antioxidant response to high oxidant status in patients with low controlled asthma. These results suggested that serum zinc levels might be a useful biomarker that supports other parameters in order to determine the level of asthma control in children. However, we think that further studies are needed to determine the importance of serum zinc levels in pediatric asthma management.

Declaration of interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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