

The relationship between serum selenium levels and frequent wheeze in children

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As an antioxidant, selenium stimulates Th1 immune response against viral infections, and may play a role in the pathogenesis of frequent wheeze due to respiratory viral infections during the first year of life.

We investigated the level of selenium in children with frequent wheeze who had no atopic diseases and no family history of atopy to determine whether selenium has an effect on the severity of the diseases.

Sixty-one children with frequent wheeze who were in the asymptomatic period and had had no infectious disease for two months and an equal number of age- and sex-matched children, as a control group, without atopy or allergy or systemic diseases were enrolled in the study. In the study group, we determined the levels of serum selenium, total IgE, mixed specific IgE, and total eosinophil count, and we performed epidermal prick tests.

Serum selenium levels were (mean and SEM) 61.95 ± 1.23 µg/L in the study group and 72.71 ± 1.28 µg/L in the control group ($p < 0.001$), and there was a negative correlation between the serum selenium levels and number of wheeze attacks during the previous year ($r = -0.655$; $p < 0.001$).

As a result, selenium may play a role in the progression of respiratory infections during childhood and can be accepted as a risk factor for development of wheezing.

Key words: children, frequent wheeze, selenium.

Allergic inflammatory disorders have been on the rise throughout industrialized countries over the last two decades. It is believed that the expression of the allergic disorders is dependent upon a genetic predisposition and environmental interactions. When the genetically predisposed individual then encounters key environmental factors, an immune/inflammatory response ensues that ultimately directs the development of allergic diseases.

In the context of environmental factors, dietary factors have been proposed to play a role both in the origin of asthma and the progression of the established diseases. In particular, a low dietary intake of antioxidants has led to an increased vulnerability of the pulmonary

airways to reactive oxygen species. Although a number of studies have suggested that there is a relationship between bronchial asthma and serum levels of certain vitamins such as vitamin C, E, A, etc.¹⁻⁶, the selenium-asthma connection seems to be stronger. The prevalence of bronchial asthma has been reported to be higher among adults who had low dietary intake of selenium⁷. Furthermore, low dietary intake of selenium during childhood has been thought to be a contributory factor in the development of asthma in later life⁸.

Besides its antioxidant characteristics, selenium also has a stimulator effect on the Th1 immune response against viral infections, and its deficiency affects the occurrence, virulence, or disease

progression of some viral infections⁹⁻¹¹. It has been demonstrated that the immune response to viral infections is skewed toward a Th2-like pattern in selenium deficiency¹¹. Furthermore, some mutations have occurred in the gene of influenza A virus under the condition of selenium deficiency¹².

On the other hand, during childhood, certain viruses have been implicated as being potentially responsible for the inception of the asthmatic phenotype. Infections with respiratory syncytial virus (RSV) has received much attention because of their predilection for producing a pattern of symptoms termed bronchiolitis, which parallels many of the features of childhood and adult asthma. The relationship between RSV infections during the first year of life and the subsequent development of the asthmatic phenotype has been a subject of both interest and controversy¹³⁻¹⁵. Atopic background is considered to be a risk factor for the development of childhood asthma, and Th2 type cytokines might be a significant predisposing factor for the development of acute bronchiolitis during RSV infections^{16,17}. If children have atopic diseases or family histories of atopy or high level of IgE and eosinophil count, RSV infection tends to be more serious, and recurrences are expected more frequently. However, RSV can also cause wheeze in some children without any risk factors. Although all children have, at some time, respiratory viral infections, why do some of them develop wheeze?

According to our hypothesis, viruses causing wheeze during childhood are RNA viruses (especially RSV, influenza A and B, parainfluenza A and B and rhinovirus), and selenium may influence the course of respiratory viral infection resulting in wheeze. In this preliminary study, we investigated the serum selenium levels in children with frequent wheeze during the asymptomatic period and the correlation with the severity of frequent wheeze.

Material and Methods

The subjects were enrolled from the pediatric asthma clinic of Hacettepe University, Faculty of Medicine, Ankara. Sixty-one children with frequent wheeze (at least 3 recurrences), aged 0.3-5 years and fulfilling the inclusion criteria, were assigned to the study group. All the

children had been in the asymptomatic period for two months and had not had any infectious disease for two months. Exclusion criteria included family history of atopy, sensitization to allergens, high level of serum IgE and eosinophilia. All other causes of airway diseases (cystic fibrosis, gastroesophageal reflux disease, tuberculosis, aspiration pneumonia, etc.) were ruled out by relevant investigations in all subjects. Severity staging was carried out as the number of attacks during the previous year. An equal number of age- and sex-matched children with minor surgical problems without atopy or systemic diseases were enrolled as controls. None of them had "ever wheeze" or infectious disease for two months.

Dietary information was collected for all children in both groups. Children with a history of malnutrition (weight for age <90% of expected) were excluded from the study. None of the patients was given any selenium supplementation four weeks before enrollment.

After obtaining parental informed consent, venous blood was taken from each subject and serum was separated by centrifugation and stored at -20°C until analysis. All samples were analyzed using spectrofluorometric method at the same time¹⁸. In the study group, we performed epidermal prick tests (milk, egg, wheat, peanut, fish, *Dermatophagoides farinae* and *pteronyssinus*, pollen, cat and dog) in order to confirm there were no atopic diseases. We determined the levels of total IgE (Pharmacia Diagnostics, CAP system, Uppsala, Sweden), mixed specific IgE (against house dust mites, cat, dog, cockroach, various grass pollens, weed pollens, tree pollens, mold spores, cow's milk, egg, wheat, peanut, soya and fish), quantitative Ig A, Ig G and Ig M, and total eosinophil count, and performed sweat test, gastroesophageal reflux (GER) scintigraphy and tuberculin tests. The children in the control group were analyzed only for total and mixed specific IgE levels.

Statistical Analysis

Distribution of data was analyzed with Leven's t test and was expressed as mean \pm standard error of the mean. Means and ratios between the two groups were compared using Student's t test and Fisher's exact chi-square test, respectively. Pearson correlation analysis was

used to determine the relationship of different variants with serum selenium levels. In each one, statistical significance was accepted when two-sided p values were lower than 0.05. All data were processed and analyzed on a computer using SPSS 11.0 for Windows.

Results

Of the 61 children enrolled in the study group, 37 were boys and 24 were girls. Their ages ranged from 4 to 54 months (median: 24 months). Nine children were under the age of 12 months. Children in the control group were similar with respect to their age, sex and nutritional status (Table I). There were also no differences according to breastfeeding period and total IgE levels between the control and study groups.

Serum selenium levels were $61.95 \pm 1.23 \mu\text{g/L}$ in the study group and $72.71 \pm 1.28 \mu\text{g/L}$ in the control group ($p < 0.001$, $95\% \text{CI} = 0.999$). Figure 1 shows the serum levels of selenium in the study and control groups.

The cut-off value of serum selenium, which was determined by using of ROC curve in the study group, was $68.6 \mu\text{g/L}$, and 82% and 40% of the patients in the study group and controls, respectively, were below the cut-off value.

A negative correlation was found between the serum selenium levels and the number of wheeze attacks during the previous year ($r = -0.655$; $p < 0.001$) (Figure 2). Age, weight, height and gender did not show any significant correlation with serum selenium levels.

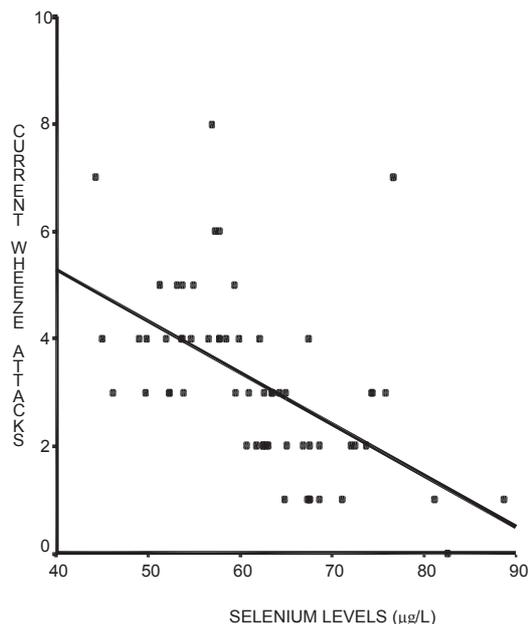


Fig. 2. Correlation between serum selenium levels and number of wheeze attacks ($p < 0.001$, $r = -0.655$).

Table I. Demographic Characteristics and Selenium and IgE Levels in Each Group

	Patients (n=61)	Controls (n=61)	P
Age* (month)	25.14 ± 1.54	22.2 ± 1.51	$P > 0.05$
Male/Female	37/24	35/26	$P > 0.05$
Height* (cm)	82.08 ± 1.03	79.38 ± 1.08	$P > 0.05$
Weight* (kg)	11.3 ± 0.21	10.74 ± 0.24	$P > 0.05$
Selenium* ($\mu\text{g/L}$)	61.95 ± 1.20	72.71 ± 1.28	$P < 0.001$
Total IgE* (kU/L)	31.28 ± 4.23	29.06 ± 5.71	$P > 0.05$

*=mean±standard error of mean.

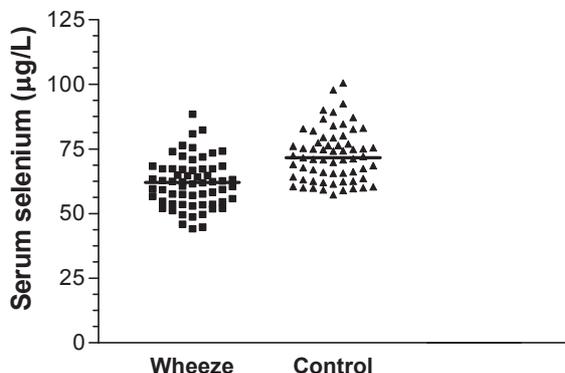


Fig. 1. Serum selenium levels of wheeze and control groups.

Discussion

In the study, we found that serum selenium levels in children with frequent wheeze were lower as compared with those in healthy controls and significantly correlated with the number of current wheeze attacks, indicating that selenium may take part in the pathogenesis of wheezing.

Although the relationship of selenium to asthma has been investigated, to our knowledge this is the first study investigating the selenium-frequent wheeze connection in the literature.

Decrease in the level of selenium may be due to either low dietary intake of selenium or increased oxidative stress. Dietary information revealed that 95% of children were breastfed for at least six months and most were consuming an adequate and balanced diet. Unfortunately, there is a lack of information regarding the selenium content of soil in Turkey. The serum levels of selenium were not affected by anti-inflammatory medication, which could minimize the use of selenium due to the increased oxidative stress. Selenium levels were still lower in children with frequent wheeze even in those using anti-inflammatory medication when compared to those in the control group (data not shown).

Besides being an antioxidant, selenium also has positive effects on the immune response against viral infections^{9,11,12,19}. Most likely, this is the most important property of selenium regarding its effects on the progression of respiratory system viral infections in children with frequent wheeze. In selenium deficiency, the immune response has been demonstrated to tend towards the Th2-like pattern against the viral infections, which leads to more severe and long-lasting inflammation in the lungs of mice during the viral infection¹¹. There are several studies showing that selenium level of the host influences the progression of Coxsackievirus, human immunodeficiency virus (HIV) and hepatitis B virus infections²⁰⁻²¹. Interestingly, the common characteristic of these viruses is their being RNA viruses. Furthermore, some mutations have been described in the viral genome in selenium deficiency, likely due to increased oxidative stress¹².

We hypothesized that all viruses causing wheeze in childhood, such as RSV, influenza A and B, parainfluenza A and B, and rhinovirus, are RNA viruses, and may cause severe bronchiolitis and frequent wheeze in some children who had no atopic diseases in the event of selenium deficiency. Interestingly, a negative correlation was found between the level of selenium and the number of wheeze attacks in our study.

The other consequence of selenium deficiency is that the increased level of Th2 type cytokines during viral infections may be a risk factor for sensitization to allergens, especially in the early years of life, and subsequently increase the development of bronchial asthma in later life.

This hypothesis may be explained by studies in which low dietary intake of selenium in childhood was determined to be a risk factor for the development of asthma, and in which asthma prevalence was found to increase in adults with a low-level intake of dietary selenium^{7,8}.

In conclusion, in countries where low level of selenium is abundant, selenium supplementation may help in achieving a better control of wheezing and selenium deficiency during childhood. Selenium deficiency may be accepted to be a risk factor for development of wheezing. More extended studies are needed to determine the correlation between low selenium levels and development of asthma in older ages.

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