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Original Article

Physiology Section

Level of Serum Selenium in Bronchial Asthma Patients in a Tertiary Care Center: A Cross-sectional Study

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ABSTRACT

Introduction: Selenium (Se) is a trace element that has role as an antioxidant in acute stress like; systemic inflammatory responses or trauma. Literature shows positive correlation between low serum Se levels and bronchial asthma.

Aim: To determine the level of serum Selenium (Se) in bronchial asthma and to compare the Se levels with the age-matched control group without asthma.

Materials and Methods: This cross-sectional study was conducted at the Departments of Physiology and Pulmonary Medicine of a Government Tertiary-care Hospital in Kerala, from November 2021 to March 2022. A total of 24 patients of Bronchial Asthma, between 20-55 years of age and 24 age-matched controls were selected. Serum Se levels were estimated in cases and controls, using Atomic Absorption Spectrometer (AAS). Statistical analysis of the data was done using unpaired sample t-test and correlation was tested with Chi-square test, using Statistical Package for Social Sciences (SPSS) version 27.0.

Results: Serum Se levels of 24 patients with Bronchial asthma, aged between 25-55 years and the Se levels in the age-matched controls were obtained. The mean Se level in the study group was (67.21±39.57 ngm/L) significantly lower (p-value was 0.0001) than that of the control (108.38±19.22 ngm/L). The mean age was 39 years±10.8 years. Out of them, 40% were females and the remaining 60% were males. The severity of Asthma ranged between mild persistent asthma to moderate asthma. And the mean duration of asthma was 5.59 years.

Conclusion: Serum Se in adult bronchial asthma patients aged between 20 years to 55 years, with mild to moderate severity was significantly lower than that in the control group.

Keywords: Antioxidant, Inflammation, Micronutrients, Stress

INTRODUCTION

Minerals and vitamins help in neutralising oxidative agents that are harmful to the cells. The role of micronutrients in proper immune function that includes inflammatory responses and antibody production is being recognised more [1]. Among the micronutrients, Selenium (Se) has a vital role in multiple aspects of human health including the thyroid function, cardiac health, prevention of cancer and neurodegenerative disorders and in maintaining proper immune functions [2]. As per a meta-analysis in the year 2019, the main source of Se (95%) in general population is diet and supplements [3]. Based on different clinical data, it has been understood that vitamins and micronutrients work together in concert for effective immune system [4]. Animal studies have shown that the deficiency of a single micronutrient can upset the immune responses [5].

Selenium is an imperative component of many anti-oxidant enzymes and has immune modulating actions [6]. These antioxidant effects of Se are carried out through its integration into Selenoproteins, which are important in controlling reactive oxygen species in almost all tissues [7]. For example, Glutathione peroxidase (GPx) is the most abundant Selenoprotein in mammals. It is a cytosolic enzyme that catalyses glutathione-dependent reduction of hydrogen peroxide to water. GPx protects the cells from lipid-peroxidation caused by the oxygen free-radicals such as superoxide and hydrogen peroxide. It is important in hydrogen peroxide signaling and maintaining cellular redox homeostasis [8,9]. So is necessary for the function of glutathione peroxidise in reducing glutathione [6].

Se deficiency can occur in viral respiratory infections. Supplementation is found to be an effective, safe and economic method to decrease the consequences of Se deficiency [4]. Bronchial asthma is a chronic inflammatory disease that has multi-factorial aetiology including oxidative stress [6]. It has been suggested that oxidative stress plays a major role in the pathogenesis of asthma. With the same notion, the possible role of antioxidants in reducing the symptoms of asthma is being considered [10].

The available literature on human studies show inconsistent and even conflicting association between the role of Se in the severity or prevalence of asthma [2,3,6,7,10]. A meta-analysis in 2019 by Chen M et al., showed that lower levels of Zn and Se are associated with increased risk of asthma [3]. Flatt A et al., in 1990 demonstrated a five-fold increase in probability of asthma in those with lower ranges of serum Se concentration [11]. Yet another study by Laustsen BH et al., among the asthmatics in seafood processing workers in Greenland, did not show association between serum Se and asthma [12]. However, they found positive association between serum Se and Forced Expiratory Reserve Volume in the first second (FEV_1). There is not much conclusive evidence from the studies that aimed at comparing the serum Se levels and the severity of asthma [3,7,10,13-15].

Animal studies using mouse models have shown definitive improvement with Se supplementation [2,5,13,16,17]. Observational studies have shown that Se levels may be low in chronic asthmatics [14]. Improvement in lung function and in the quality of life with Se supplementation, probably by reducing the oxidative stress was demonstrated in asthmatics [18]. Hence, a multidisciplinary approach is warranted to comprehend the complex relationship between the nutrients and bronchial asthma [19]. However, Se supplementation has not yet been recommended in the management of bronchial asthma [20].

Low Se level is thought to be a potential risk factor for severity or increased prevalence of asthma, based on the role of Se as an immune modulator and as an antioxidant. The two-fold effects of Se in regulating the T helper cells in allergic asthma and controlling oxidative stress in the lungs, apart from its incorporation to the Selenoproteins need to be considered while unfolding the relationship between asthma and micronutrients [21]. It is possible that higher

intake of Se can curtail inflammation in asthma by optimising the activity of Selenoproteins like GPx [8]. This enzyme catalyses the antioxidant Glutathione in the airway epithelium, which plays an essential role in protection from oxidative stress.

MATERIALS AND METHODS

This was a cross-sectional study conducted at the Departments of Physiology and Pulmonary Medicine of the Government Medical College, Thrissur, Kerala, India. After obtaining the Institutional Ethical Clearance (IEC No: IEC/GMCTSR/196/2021), the duration of the study was November 2021 to March 2022. Among the micronutrients, the authors considered estimation of serum Se because asthma is an inflammatory condition caused by oxidative stress and also because Se is an integral component of Selenoproteins, which are proven antioxidants in tackling such inflammatory conditions.

Inclusion criteria: A total of 24 bronchial asthma patients, both male and female aged between 20-55 years, attending the pulmonary medicine Out-patients Department (OPD) were selected. The mean duration of Bronchial asthma among the cases was 5.59 years and their age-matched controls who were devoid of asthma were taken as controls. The severity of asthma ranged between mild persistent asthma to moderate asthma. Severity was assessed based on the presence/absence of the following criteria [22,23];

- Breathlessness: on exertion, affecting activities of daily life, night-time flare-up {Paroxysmal Nocturnal Dyspnoea (PND)}, breathlessness while lying down (Orthopnoea);
- Frequency of symptoms: daily or how many times per week;
- Use of rescue medicines daily or how many times per week;
- Hospitalisation required or not, number of admissions.

Exclusion criteria: Pregnancy, renal diseases, liver diseases, diarrhoea, vomiting.

Those with the criteria present were categorised as persistent moderate asthma. Those who were having symptoms daily,those having PND, those using rescue medicines (beta agonists) daily and those having some limitations in their daily activity were grouped as moderate persistent asthma [22]. Those with <2 attacks/ week, without PND, using medicines twice/week were grouped as mild persistent asthma [22].

Sample size calculation: Sample size was calculated using the formula:

$n=\{2\sigma^2(Z\alpha+Z\beta)^2\}\div d^2$

$d=\mu_1-\mu_2,\ \sigma^2=(SD_1^2+SD_2^2)\div 2$

$(Z\alpha+Z\beta)^2=(1.96+0.84)^2=7.84$; $Z\alpha$ is the value of α error at 95% confidence interval, $Z\beta$ is the value of β error when power is 80%, μ_1 is the mean value of cases, μ_2 is the mean value of controls. SD1 is the standard deviation in cases and SD2 is the standard deviation in controls. Sample size was calculated as 23 from the reference study by Vural H et al., and thus 24 bronchial asthma patients and 24 controls (subjects without asthma) were included in the study [24].

Procedure

After de-identifying the data, the patient profile data were entered in Microsoft Excel. Subsequently blood samples were collected from the study subjects and the controls. Serum was separated from the blood samples on a daily basis. Serum samples were transported to the Central Laboratory of Government, Veterinary College, maintaining the temperature specifications [24]. Serum Se levels were analysed using AAS Spectrometer (Model: PinAAcle 900H0). The method used was Flame analysis (fuel/oxidant: Acetylene (2.5 L/min)/Air (10 L/min) method with Hollow Cathode Lamp [25]. The results were tabulated. The cut-off value for lower limit of normal Se levels was taken as 70 ngm/L [26,27].

STATISTICAL ANALYSIS

The SPSS software version 27.0 was used for the statistical analysis. For quantitative variables, mean, standard deviation and unpaired t-tests were used. For qualitative variables, odds ratio was used. Chi-square test and Fisher's-exact tests were used to detect the significance. Two-sided significance was considered for each. All p-values of <0.05 obtained from two-sided tests were considered significant.

RESULTS

Total 24 bronchial asthma patients were studied along with their age-matched controls. Their age was between 20 years to 55 years and the mean age was 39±10.8 years. Severity of asthma ranged between mild-persistent to moderate asthma. Patients were under treatment with inhalational and oral short acting beta agonists.

Among the asthmatic group, 37.5% were females and the remaining 62.5% were males. The control group consisted of 58.33% males and the remaining were females. The duration of asthma was between 2 years to 5 years and the mean duration was 5.59 years [Table/Fig-1].

	Age (mean)	SD (years)	p-value	Male n (%)	Female n (%)	Mild asth-ma	Moder-ate asthma	Dura-tion
Case	40.86 years	10.02	0.498	15 (62.5%)	9 (37.5%)	14 (14%)	10 (41.66%)	5.59 years
Control	39.39 years	11.29	0.499	14 (58.33%)	10 (41.67%)	-	-	-

[Table/Fig-1]: Distribution of age, gender, duration and severity of asthma among the study participants.

The mean Se level in the study group was (67.21±39.57 ngm/L) was significantly low than the control (108.38±19.22 ngm/L). The mean serum Se levels in both the groups were compared using Unpaired-sample t-test [Table/Fig-2] and the p-value was 0.0001, which is statistically significant.

	No. of samples	Mean serum Se
Patients	24	67.212±39.57 ngm/L
Control	24	108.375±19.22 ngm/L
p-value	**0.0001**	

[Table/Fig-2]: Mean Se levels, compared using Unpaired sample T test the mean Se levels among the cases and controls.

The odds ratio was calculated between the low serum Se levels and Bronchial asthma and the p-value was 0.04 [Table/Fig-3] that indicates a significant association between low Se levels and Bronchial asthma.

Name of test	p-value	95% confidence upper	95% confidence lower
Pearson Chi-square	**0.001**	-	-
Fisher's-Exact Test	**0.001**	-	-
Odds Ratio: Low Se and Asthma	**0.040**	**0.004**	0.356

[Table/Fig-3]: Pearson Chi-square, Fisher's Exact test and Odds Ratio indicating the respective p-values.

DISCUSSION

In this study, the authors aimed at obtaining the serum profile of Se in Bronchial asthma and finding out if there is any association between low Se levels and Bronchial asthma. The Se levels were low in patients with asthma when compared to their age matched controls. Results of the present study also showed that lower Se levels had positive correlation with Bronchial asthma. This indicates that lower serum Se levels are associated with systemic inflammatory response where the antioxidants like Selenoproteins are involved.

A British study by Stone J et al., found lower Se concentration in red blood cells and plasma in asthmatic patients, in comparison to the

normal subjects [28]. Their study on forty nine asthma patients and seventy six healthy controls demonstrated significant association between low Se levels and Bronchial asthma. In that study, Se concentration in the plasma, whole blood and in platelets was measured along with GPx activity. The odds ratios showed four-fold increase in probability of Bronchial asthma in those with low plasma Se and a five-fold increase in probability with low Se in the whole blood. Their study also concluded that there was significant association between low Se levels and symptomatic asthma [28].

A postmortem study conducted by Dunnill MS in the year 1959, on twenty patients who died with status asthmatics has described the inflammatory nature of Bronchial asthma [29]. In their study, the histo-pathology specimens showed exudates apart from other features of asthma like prominent sub-mucosal inflammation. He also mentions about Wilhem, who demonstrated inflammation of the tracheal submucosa in asthmatics in 1953 itself. Flatt A et al., in their study has shown that the whole blood selenium concentrations and GPx activity were lower in asthmatic patients, when compared to the non-asthmatic control population [11]. They demonstrated a two-fold increase in relative risk of asthma in those with the lowest levels of whole blood Se. Those with lowest levels of GPx activity showed a six-fold relative risk of Bronchial asthma [11]. Low levels of GPx activity can increase the risk of asthma. It can cause worsening of the airway inflammation by two possible mechanisms; reduced protection against free radical injury and inadequate regulation of the Lipoxigenase pathway [29].

In a Korean study published in 2016, they selected ninety one patients with respiratory diseases and divided them into two groups (the Intensive Care Unit (ICU) group and the general ward group), based on the criteria for acute infectious or inflammatory respiratory disorders [30]. Patients with asthma, pneumonia, chronic obstructive pulmonary disease, adult respiratory distress syndrome; together termed as Systemic Inflammatory Response Syndrome (SIRS) were included.

The study aimed at finding the association between the serum Se levels and the severity of respiratory disease by comparing that of the patients in ICU and in general ward. The serum Se level was 70±26 ng/mL in the ICU group and 98±21 ng/mL in the general ward group of SIRS patients, when compared to the Se levels of the healthy Koreans (112±30 ng/mL). Se levels were found significantly lower in the critically ill patients with SIRS, also indicating that the decrease in Se level was correlated with the severity of the disease [30].

In the present study, as well, the authors found that the mean serum Se in the patients with Bronchial asthma was 67.21±39.57 ngm/L, which was significantly lower when compared to the Se levels in the control group (108.38±19.22 ngm/L) without asthma. However, the authors did not look for the correlation between the low Se levels and the severity of asthma, unlike how Lee YH et al., did in their Korean study. In a previous study conducted in the year of 2014, the effect of serum Se on the outcomes of critically ill surgical patients was investigated, retrospectively [30]. Mean selenium concentrations were significantly low in patients with shock (77.9±25.4 ng/dL) than those without shock (87.2±23.1 ng/dL). And mean Se was significantly lower in patients with sepsis than those in without sepsis among postoperative patients [31].

In yet another study, plasma and urine Se levels were measured in thirty one patients with Systemic inflammatory response syndrome (SIRS), during their ICU admission. The values were compared with the laboratory reference values and also with the severity of SIRS. Se levels were lower in those with SIRS when compared to those without SIRS [32]. Their study also showed a slight increase in Se levels in those who survived SIRS and it decreased in those who failed to survive. The decline in Se concentration (by 40%) in those SIRS patients in ICU were close to the Se levels of those having severe nutritional deficiency of Se. This probably explains the three-fold increase in morbidity and mortality in those with severe nutritional Se deficiency [32]. Hawker FH et al., were the first ones to report significantly lower Se levels in ICU patients in comparison to the healthy controls in 1990 [33]. Their study also indicates the role of Se as an antioxidant in acute stress and inflammation.

There are inconclusive evidence in the literature, regarding the role of Se in asthma. The above studies demonstrated the role of Se in acute inflammatory conditions like SIRS including asthma and in ICU patients [11,12,28,30-32]. Likewise in the present study also, the serum Se levels were significantly lower in patients with Bronchial asthma, when compared to their age-matched controls without asthma. So this present study adds to the literature that there is a positive correlation between the low serum Se levels and acute inflammatory conditions like Bronchial asthma in this part of the Indian population. Though the authors have not assessed the difference in Se values in relation with the severity of Bronchial asthma, some of the studies [31-33] have demonstrated the association between the low Se levels and severity of the illness. So evidence weighs more towards the significant role of Se in acute inflammation. The present study also shows the positive correlation between the lower Se levels and asthma and hence it contributes to the literature for the protective role of Se in acute inflammatory conditions.

Limitation(s)

The correlation of low Se levels with the severity of bronchial asthma was not included in this study.

CONCLUSION(S)

Selenium is a trace element that has role as an antioxidant in acute stress like; systemic inflammatory responses or trauma. Evidence weighs more towards the role of Selenium in the severity or prevalence of asthma. In the present study, the authors found that the serum Selenium in bronchial asthma is significantly lower than that in the control group. In addition to that, there was a positive association between lower Se levels and asthma, which was statistically significant. This throws light into the role of Se in control of inflammation as in bronchial asthma patients, possibly a protective role of Selenium. However, further studies are required to elucidate the role of Se in asthma and to find out whether Se supplementation has a role in the management of asthma.

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