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CALCIUM AND IRON STATUS IN ASTHMA PATIENTS

Dr.V.Umalakshmi [1]M.D, *Dr.K.Bhargavi[2]M.D, Dr.V.RatnaKumari[3]M.D, Dr.M.GouriDevi[4]M.D

[1]Professor, Department of Biochemistry, Osmania Medical College, Hyderabad, Telangana, India.

[*2]Senior Resident, Department of Biochemistry, Osmania Medical College, Hyderabad, Telangana, India.

[3,4]Assistant Professor, Department of Biochemistry, Osmania Medical College, Hyderabad, Telangana, India.

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***Correspondence for Author**
Dr. Kareti Bhargavi
Senior Resident, Department of Biochemistry, Osmania Medical College, Hyderabad, Telangana, India.

ABSTRACT

Introduction: Asthma is associated with airway hyperresponsiveness correlated with variable airflow obstruction. Calcium is the second messenger regulating airway smooth muscle contraction. Abnormalities in calcium homeostasis is manifested by increase flux of calcium and alteration in calcium regulatory proteins playing a critical role in airway smooth muscle hyperactivity in asthma. Iron metabolism is of crucial importance in the pathophysiology of the lower respiratory tract. **Aim:** To measure the levels of serum Calcium, serum Iron in patients with stable asthma and exacerbating asthma and to predict the severity of asthma. **Materials & Methods:** A case control study of 120 was conducted including 40 controls, 40 of Stable Asthma Group and 40 of Exacerbating Asthma patients. **Results:** Showed significant increase of Calcium ($p<0.0001$) in asthma with exacerbation (20.89 ± 2.32) compared to that of control group (9.618 ± 0.86). Serum Iron ($p<0.0001$) in patients of asthma with Exacerbations (201.73 ± 11.59) compared to that of control (111.8 ±12.21).No statistical significance was observed in Stable asthma when compared to controls. **Conclusion:** Calcium and Iron levels increased significantly in Exacerbating asthma when compared to Stable asthma patients.

KEYWORDS: Calcium, Iron, Exacerbating Asthma, Stable Asthma.

INTRODUCTION

Asthma is one of the most common chronic disease globally and affects 300 million people worldwide. It is a chronic reversible, inflammatory disease of the airways.It is a heterogenous disease with interplay between genetic and environmental factors.

Calcium is an important mineral and most prevalent cation in intracellular and extracellular fluid.In serum, calcium exists as free and bound form.[1,2] Calcium is the second messenger regulating airway smooth muscle contraction. Abnormalities in calcium homeostasis is manifested by increase flux of calcium and alteration in calcium regulatory proteins playing a critical role in airway smooth muscle hyperactivity in asthma.[3,4] Calcium plays an important role in excitation and muscle contraction and stabilizes the plasma membrane influencing permeability and excitability.Extracellular calcium functions as ionic chemo kinetic agents capable of modulating the innate immune response by direct and indirect action on monocytes.[5] Calcium deposition may be both consequence and cause of chronic inflammatory changes at the site of injury and infection.[3,5]

The cell electrolyte composition changes in Bronchial asthma, impairing the c AMP metabolism and activating the lipid peroxidation.[3,6] leading to bronchial hyperactivity. The abnormal intracellular homeostasis of bivalent cation in asthmatic patients may be due to hyperactivation of free radical oxidation of cell membrane lipids.[6] Calcium in cytoplasm is cytotoxic, therefore necessary to regulate calcium overload. Excessively generated oxidation, reperfusion injury, changes mitochondrial function and cause calcium leak from organelle which leads to apoptosis.[3,7]

Iron is a critical element for the function of the cell,although the amount of iron required by individual tissues varies.[8] Free iron being highly toxic generates free radicals such as singlet O_2 or OH^-.Asthma is a chronic inflammatory disease of airways and reactive oxygen species[9] the presence of iron binding proteins in different lung compartments contributing to increased incidence of asthma.[3,10]

MATERIALS AND METHODS

The study was conducted in Department of Biochemistry, Osmania General Hospital. A case control study of 120 divided into three groups including 40 controls, 40 cases of Stable Asthma Group and 40 cases of Exacerbating Asthma group. Patients with history of respiratory infection, pneumonia, chronic bronchitis, coronary heart disease, heart failure,

neuromuscular disease, renal and hepatic dysfunction were excluded.5ml of blood was taken in plain vaccutainer. Grossly hemolysed and lipemic samples were excluded.

The data was analysed using Graph Pad Prism 5.01 software version and SPSS (Statistical package for social science) and the results were expressed as Mean and Standard deviation of various parameters in different groups. Multiple comparisons ANOVA was used to assess the significance of difference of mean values of different parameters in between the groups. The significance of difference of mean values of different groups and within the groups is represented by p values and p value <0.05 is considered as significant.

Serum Calcium is estimated by Ocresolphthalein Conaplexone (CCPC) method in semiautoanalyser.[11,12,8,13,4] and serum iron estimated by Ferrozine method(colorimetric procedure).[14,15,16]

RESULTS

In the present study, there was statistically significant increase ($p<0.0001$) in the mean value of serum Calcium in asthma with exacerbation (20.89 ± 2.32) compared to that of control group (9.618 ± 0.86). No statistical significance was observed between stable asthma patients (8.94 ± 1.23) and control group.

There was statistically significant increase ($p<0.0001$) in the mean value of serum iron.No statistical significance was observed between stable asthma patients (101.408±10.78) and control group.(Table-1)

Table-I. Mean, Standard Deviation and Significance of various parameters in asthma patients.

Parameters	Mean ± SD of Controls	Mean ± SD of stable asthma cases	Mean ± SD of exacerbating asthma cases
Calcium	9.618 ± 0.86	8.94 ± 1.23	20.89 ± 2.32*
Iron	111.8±12.21	101.48 ±10.78	201.73± 11.59*

**p value less than (0.0001)*

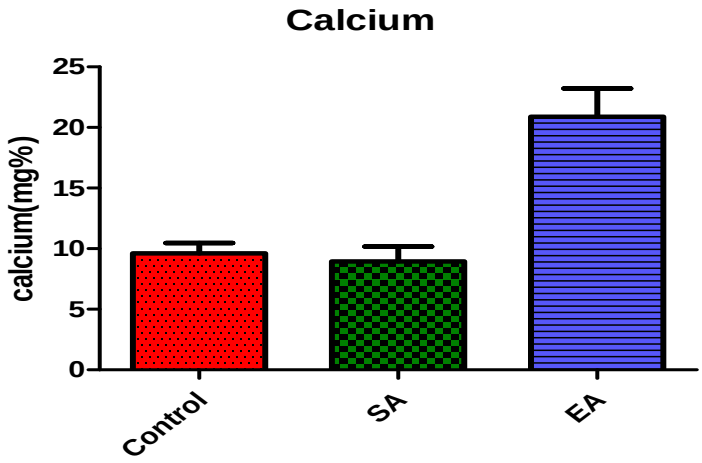

Fig-I: Comparison between Serum Calcium in Stable Asthma (SA) and Exacerbating Asthma (EA) patients.

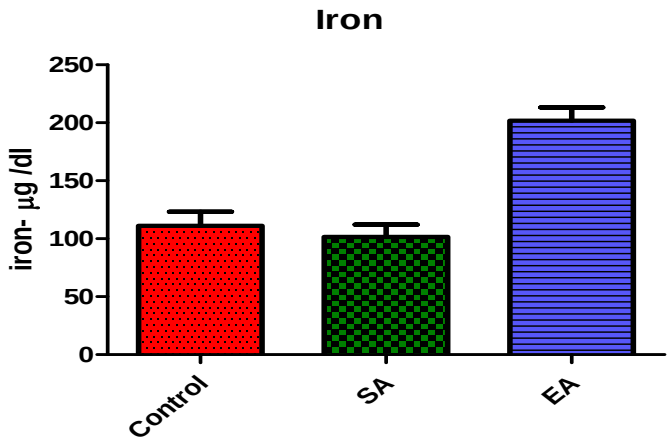

Fig II: Comparison between Serum Iron in Stable Asthma (SA) and Exacerbating Asthma (EA) patients.

DISCUSSION

Asthma is a chronic inflammatory disorder of the air ways. The strongest identifiable predisposing factor for the development of asthma is atopy, but obesity is increasingly recognized as a risk factor. Exposure of sensitive patients to inhaled allergens increases airway inflammation, airway hyper-responsiveness, and symptoms. This airway inflammation underlies disease chronicity and contributes to airway hyper-responsiveness, airflow limitation and respiratory symptoms including recurrent episodes of wheezing, breathlessness, chest tightness and cough.

Airway Hyperresponsiveness (AHR) is the characteristic physiological abnormality of asthma and describes the excessive bronchoconstrictor response to multiple inhaled triggers that would have no effect on normal airways. The increase in AHR is linked to the frequency of asthma symptoms and thus, an important aim of therapy is to reduce AHR. Increased bronchoconstrictor responsiveness is seen with direct broncho constrictors but is characteristically also seen with many indirect stimuli, which release bronchoconstrictors from mast cells or activate sensory nerves. Most of the triggers for asthma symptoms appear to act indirectly, including allergens, exercise, hyperventilation, fog(via mast cell activation) irritant dusts and sulfur dioxide (via a cholinergic/ reflex**)**

Pathogenic mechanism of lung injury has focused on the cellular and biochemical mediators to be considered as potential biological markers of lung injury. The findings in the study are associated with increased duration of diseases with chronic inflammation of lower airways. Thus the present study suggests that the existence of inflammation in the airways and hyperirritability of airway mucosa contributes to remission of attack when exposed to allergens and reduce the success rate of treatment and recovery of the patient.

The parameter were analysed into three groups,40 stable asthma cases,40 exacerbating asthma cases and 40 non asthmatic healthy controls. These findings were associated more with increased inflammation of the airways, the mucosa gets infiltered with inflammatory cells like mast cells, eosinophils, neutrophils,[3,17] lymphocytes, macrophages and inflammotry mediators like histamine, leucotriene, cytokines, chemokines which leads to airway hyperresponsiveness and mucous secretion which leads to structural changes and bronchospasm. Myer and Zimmerman[3,18] reported that there was alteration of surfactant composition and function in various inflammatory disorders that affect the airways or the lung parenchyma including asthma.

Calcium ions (Ca^{2+}) are fundamental to the process responsible for the initiation and maintenance of contraction of ASM cells and development in understanding of signal transduction mechanisms relating to intracellular Ca^{2+} release, excitation - contraction coupling mechanisms in ASM.[3,19] Serum calcium concentration was in excess in bronchial asthma irrespective of asthma variant, phase severity and bronchial obstruction.[3,6] These study findings indicate a positive relation between serum calcium levels and disease severity as shown by the high level during exacerbation as compared to stable asthma.

Calcium levels were lower in asthma patients who have been treated and this could be due to the hyposensitization which has regulated cytokine production inhibition of phospholipase C and / or modulation of oxidant activity generated by effector cells and consequently affect serum calcium.[7,20] Calcium is the second messenger regulating airway smooth muscle contraction, abnormalities in calcium homeostasis manifested by increases in the flux of calcium or alteration in calcium regulatory proteins, may play a critical role in inducing airway smooth muscle hyperreactivity in asthma.The abnormalities in Iron homeostasis causing excessive accumulation of iron leads to generation of potentially toxic hydroxyl radicals which contributes to the risk of asthma attack.

In the present study it was observed that there is statistically significant increase ($p < 0.0001$) in the mean value of serum Calcium in patients of Asthma with exacerbation(20.89 ± 2.32) compared to that of control group (9.618 ± 0.86).However no statistically significant difference has been observed between stable asthma patients (8.94± 1.23) and control group.The present study suggests that the serum calcium concentration in exacerbating asthma is higher than that of stable asthma patients. In an initial study Gugger et al reported that in bronchial asthma an alteration of calcium metabolism may be important.[3,19]

Iron metabolism is of a crucial importance in the biology and pathophysiology of the lower respiratory tract.[3,24] As with many other factors involved in inflammation,it is very important that an appropriate iron balance is maintained. Local deficiency could impair growth and proliferation of cells responsible for the inflammatory response and tissue repair and the synthesis of mediators. In contrast, excessive accumulation of iron, especially in free form that is not bound to one of the specific iron-binding proteins facilitates the generation of potentially toxic hydroxyl radicals.[3,25]

From the present study it was observed that there is statistically significant increase ($P< 0.0001$) in the mean value of serum Iron in patients of Asthma with exacerbation (201.73 ± 11.59) compared to that of control group (111.08 ± 12.21).However no statistically significant difference has been observed between Stable asthma patients (101.48 ±10.78) and control group. The present study suggests that the serum Iron concentration in exacerbating asthma is higher than that of stable asthma patients.[21,22] Vural et al reported that serum iron level in asthmatics were not significantly different from control group.[3,23]

In the present study there was a statistically significant increase in the serum levels of Calcium & Iron in Exacerbating asthma compared to that of controls and Stable asthma patients. Hence the evaluation of these parameters can be of benefit in the prognosis of the disease and are helpful to guide clinicians regarding the treatment.

CONCLUSION

Asthma is a chronic inflammatory disease of airways. It is a heterogenous disease with several different phenotypes and it is generally triggered by multiple gene and environment interactions. Asthmatics develop a special type of inflammation in the airways that makes them more responsive than non-asthmatics to a wide range of triggers leading to limitation of airflow due to bronchoconstriction, but airway edema, vascular congestion, and luminal occlusion with exudate also contributes to it. The various triggers involved in asthma are atopy, indoor allergens, outdoor allergens, airway hyper responsiveness, occupational sensitizers, passive smoking, gender, obesity, ethnicity, respiratory tract viral infections, exercise and hyperventilation. Inhaled allergens are common triggers of asthma symptoms in allergic sensitization. Exposure to house dust mites in early childhood is a risk factor for allergic sensitization and asthma.

In the present study the above parameters were evaluated to distinguish between Stable asthma and Exacerbating asthma cases. The Exacerbating asthma cases are those who showed significant increase in Serum Calcium and Iron whereas Stable asthma cases are those who showed normal levels of Calcium and Iron.

To conclude from the present study, Serum Calcium and Iron were measured in Exacerbating asthma and Stable asthma cases to correlate these levels and predict the risk of severity of asthma to help the clinician in diagnosis and implementation of appropriate treatment and prevent the risk of sudden and severe airway obstruction in those with hyperirritability of airways and other allergic diseases who are at high risk for development of fatal asthma.

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